Product Monograph

Including Patient Medication Information

NAROPIN®

Ropivacaine hydrochloride for epidural infusion

Sterile and isotonic solution

For infiltration, nerve block and epidural use

2 mg/mL of ropivacaine hydrochloride

Ropivacaine hydrochloride injection

Sterile and isotonic solution

For infiltration, nerve block and epidural use

5 mg/mL of ropivacaine hydrochloride

Ropivacaine hydrochloride injection

Sterile and isotonic solution

For epidural use

10 mg/mL of ropivacaine hydrochloride

Manufacturer Standard

Local anesthetic

Aspen Pharmacare Canada Inc

201 - 2030 Bristol Circle

Oakville, ON, L6H 0H2

Date of Authorization:
2025-09-22

Control Number: 295134

Recent Major Label Changes

7 Warnings and Precautions, Monitoring and Laboratory Tests	2024-10
7 Warnings and Precautions, 7.1.1 Pregnancy	2025-09

Table of Contents

Certain sections (as indicated in section 2.1. of the PM Guidance) or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1 Indications

NAROPIN (ropivacaine hydrochloride) is indicated for:

Analgesia

Acute pain management in connection with:

- Continuous epidural infusion or intermittent bolus administration e.g., postoperative or labour pain;
- Field block e.g., infiltration

Anaesthesia

Surgical anaesthesia in connection with:

- Epidural block for surgery, including Caesarean section;
- Major nerve block e.g. brachial plexus block;
- Field block e.g. infiltration

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (> 65 years of age): Elderly patients should be given reduced doses of ropivacaine, commensurate with their age and physical condition (see 7.1.4 Geriatrics and 4.1 Dosing Considerations).

2 Contraindications

NAROPIN (ropivacaine hydrochloride) is contraindicated:

- in patients with a hypersensitivity to ropivacaine or to any ingredient in the formulation or component of the container (see 6 Dosage Forms, Strengths, Composition and Packaging).
- in patients with hypersensitivity to any other local anaesthetic agent of the amide type.
- for intravenous regional anaesthesia (Bier block).
- in obstetric paracervical block anaesthesia. Use of other local anaesthetics in this technique has resulted in fetal bradycardia and death.

3 Serious Warnings and Precautions Box

- Local anaesthetics should only be used by healthcare professionals who are well versed in

diagnosis and management of dose-related toxicity and other acute emergencies which may arise from the block to be performed, and then only after ensuring the immediate availability of cardiopulmonary resuscitative equipment, resuscitative drugs, including oxygen, and the personnel resources needed for proper management of toxic reactions and related emergencies (see 8 Adverse Reactions and 5 Overdosage). 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.

- In performing NAROPIN (ropivacaine hydrochloride) blocks, unintended intravascular or subarachnoid injection is possible and may result in cardiac arrhythmia or cardiac arrest. The potential for successful resuscitation has not been studied in humans.

- NAROPIN should be administered in incremental doses. It is not recommended for emergency situations, where a fast onset of surgical anaesthesia is necessary.

  Solutions of NAROPIN should not be used for the production of retrobulbar block or spinal anaesthesia (subarachnoid block) due to insufficient data to support such use.

4 Dosage and Administration

4.1 Dosing Considerations

General

NAROPIN should only be used by or under the supervision of health professionals experienced in regional anaesthesia.

It is recommended that hospitals using local anaesthetic infusions have a treatment protocol in place in order to safely monitor the level of the block and for the proper management of complications and/or toxic reactions. If toxic reactions occur, the infusion should be stopped immediately.

There have been adverse event reports of irreversible chondrolysis in patients receiving intra-articular infusions of local anaesthetics following arthroscopic and other surgical procedures. NAROPIN is not approved for this use (see 7 Warnings and Precautions, General).

NAROPIN should be administered at the smallest dose and the lowest concentration which are consistent with the necessary degree of anaesthesia or analgesia. The rapid injection of a large volume of local anaesthetic solution should be avoided and fractional doses should always be used. In general, surgical anaesthesia, e.g. epidural administration, requires the use of higher concentrations and doses. For analgesia, e.g. epidural administration for acute pain management, lower concentrations and doses are recommended.

The dose of any local anaesthetic administered varies with the anaesthetic procedure, the area to be anaesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anaesthesia and degree of muscle relaxation required, the duration of anaesthesia desired, individual tolerance, and the physical condition of the patient.

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

Special Populations

Local anaesthetics should be used with caution in patients in poor general condition due to advanced age, debilitation, or other compromising factors such as partial or complete heart conduction block, advanced liver disease, or severe renal dysfunction. To reduce the risk of potentially serious adverse reactions, attempts should be made to optimize the patient's condition before major blocks are performed. Elderly and acutely ill patients should be given reduced doses of ropivacaine, commensurate with their age and physical condition.

4.2 Recommended Dose and Dosage Adjustment

Adults (>18 years of age): The dosages in Table 1 are recommended as a guide for use in the average adult for the more commonly used blocks. The healthcare professional's experience and knowledge of the patient's physical status are of importance in calculating the required dose.

Table 1 - Adult dosage recommendations for NAROPIN

TYPE OF BLOCK	CONC. (mg/mL)	VOLUME (mL)	DOSE (mg)
ACUTE PAIN MANAGEMENT			
Lumbar Epidural Bolus (initial dose) Intermittent injections (top-up) *e.g.,* labour pain management	 2 2	 10-20 10-15 (minimum interval 30 minutes)	 20-40 20-30
Lumbar Epidural Continuous infusion *e.g.,* labour pain and postoperative pain management	2	6-14 mL/h	12-28 mg/h
Thoracic Epidural Continuous infusion *e.g.,* postoperative pain management	2	6-14 mL/h	12-28 mg/h
Field Block *e.g.,* infiltration	 2 5	 1-100 1-40	 2-200 5-200
SURGICAL ANAESTHESIA			
Lumbar Epidural Surgery Caesarean Section	 5 10 5	 15-30 15-20 20-30	 75-150 150-200 100-150
Thoracic Epidural To establish block for postoperative pain management.	5	5-15	25-75
Major Nerve Block *e.g.,* brachial plexus block	5	35-50	175-250[1]

TYPE OF BLOCK	CONC. (mg/mL)	VOLUME (mL)	DOSE (mg)
Field Block *e.g.,* infiltration	5	1-40	5-200

Note 1: 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. The figures reflect the expected average dose range needed. For other local anaesthetic techniques standard textbooks should be consulted.

Note 2: There have been post-marketing reports of irreversible chondrolysis in patients receiving post-operative intra-articular infusion of local anaesthetics. NAROPIN is not approved for this use (see 7 Warnings and Precautions, General).

[1] The dose for a major nerve block must be adjusted according to site of administration and patient status. Interscalene and supraclavicular brachial plexus blocks may be associated with a higher frequency of serious adverse reactions, regardless of anaesthetic used.

Careful aspiration before and during injection is recommended to prevent intravascular injection. When employing an epidural block, a test dose of 3-5 mL lidocaine (XYLOCAINE 1-2%) with epinephrine is recommended. An inadvertent intravascular injection may be recognized by a temporary increase in heart rate and an accidental subarachnoid injection by signs of a spinal block. Aspiration should be repeated prior to and during administration of the main dose, which should be injected slowly or in incremental doses, at a rate of 25-50 mg/min, while closely observing the patient's vital functions and maintaining verbal contact. If toxic symptoms occur, the injection should be stopped immediately. The test dose should be repeated if the patient is moved in such a fashion as to have displaced the epidural catheter.

In epidural block for surgery (excluding Caesarean section), single doses of up to 250 mg ropivacaine have been used and are well tolerated.

In epidural block for Caesarean section, an initial epidural dose of up to 150 mg (25 mL NAROPIN 5 mg/mL) injected over 5 minutes is well tolerated (see 7 Warnings and Precautions, General). For Caesarean section, neither the use of ropivacaine concentration 10 mg/ mL (for epidural administration) nor intrathecal administration have been documented.

For treatment of postoperative pain, the following technique is recommended: Unless preoperatively instituted, an initial epidural block with NAROPIN 5 mg/mL is induced via an epidural catheter. Analgesia is maintained with NAROPIN 2 mg/mL infusion. Clinical studies have demonstrated that infusion rates of 6-14 mL (12-28 mg) per hour provide adequate analgesia with only slight and non-progressive motor block in most cases of moderate to severe postoperative pain. With this technique, a significant reduction in the need for narcotics has been observed. Clinical experience supports the use of NAROPIN epidural infusions at rates up to 28 mg/h for 72 hours.

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. Clinical experience to date indicates that a cumulative dose of up to 770 mg ropivacaine administered over 24 hours and continuous epidural infusion at rates up to 28 mg/h for 72 hours have been well tolerated in adults when used for postoperative pain management (i.e., ≥2000 mg).

The duration and intensity of ropivacaine block are not improved by the addition of epinephrine.

Pediatrics (< 18 years of age): The safety and efficacy of NAROPIN have not been investigated in pediatric patients. NAROPIN is not indicated for use in patients below the age of 18 years.

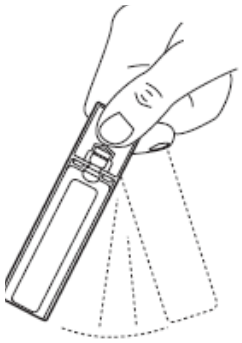
4.4 Administration

Instructions for Use

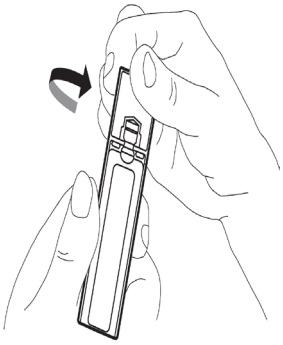
Polyamp

No needle is required to withdraw the solution.

1. Hold tab of Polyamp and flick down firmly to remove contents from the neck.

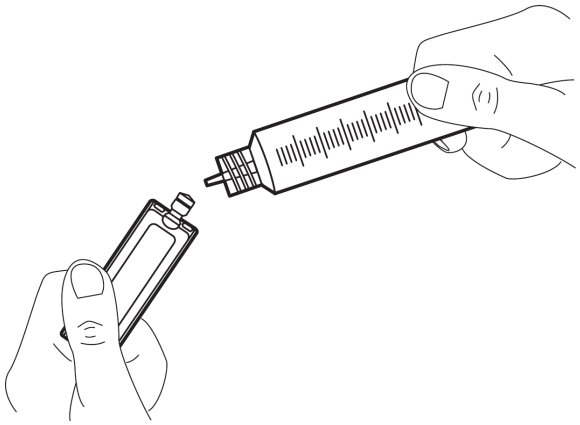


2. Hold Polyamp by the shoulders and remove the top with a twisting action. Do not squeeze while opening.



3. Prior to connecting the Luer syringe tip to the Polyamp neck, fill the syringe with the volume of solution to be withdrawn

4. Connect Luer syringe tip to Polyamp neck. Push firmly and twist to ensure a snug fit to avoid leakage



5. Inject air into Polyamp

Drug Compatibilities

NAROPIN for infusion in polypropylene infusion bags (Polybag) is chemically and physically compatible with the following drugs:

Concentration of NAROPIN: 1-2 mg/mL	
Drug solution	**Concentration**
Fentanyl citrate	1 – 10 mcg/mL
Sufentanil citrate	0.4 – 4 mcg/mL
Morphine sulphate	20 – 100 mcg/mL
Clonidine hydrochloride	5 – 50 mcg/mL

The mixtures should be used immediately. As with all parenteral products, intravenous admixtures should be visually inspected for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should be discarded.

Incompatibility

Alkalinization may lead to precipitation since ropivacaine is poorly soluble above pH 6.

5 Overdose

Systemic toxic reactions primarily involve the central nervous system and cardiovascular system. Such reactions are caused by high plasma levels encountered during therapeutic use, overdose, or to unintended intravascular or subarachnoid injection (see 7 Warnings and Precautions, and 8 Adverse Reactions). Central nervous system reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively.

Symptoms

Accidental intravascular injections may cause immediate (within seconds to a few minutes) toxic effects. In the event of overdose,

- for single injection: systemic toxicity appears later (15 – 60 minutes after injection) due to the slower increase in local anaesthetic blood concentration.
- for repeat dosing or continuous infusion: peak plasma concentrations may not be reached for 1 to 2 hours, with signs of toxicity thus being delayed.

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity.

- First symptoms are usually light-headedness, circumoral paraesthesia, numbness of the tongue, hyperacusis, tinnitus and visual disturbances.
- Dysarthria, muscular rigidity and muscular twitching are more serious and may precede the onset of generalized convulsions. These signs must not be mistaken for a neurotic behaviour.
- Unconsciousness and grand mal convulsions may follow which may last from a few seconds to

several minutes.

- Hypoxia and hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with normal respiration and loss of the airway. In severe cases apnoea may occur.

Acidosis, hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

Recovery is due to redistribution and metabolism of the local anaesthetic drug. Recovery may be rapid unless large amounts of the drug have been administered.

Cardiovascular system toxicity indicates a more severe situation and is generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anaesthetic or is heavily sedated with drugs such as a benzodiazepine or barbiturate. Hypotension, bradycardia, arrhythmia and cardiac arrest may occur as a result of high systemic concentrations of local anaesthetic. In volunteers, the intravenous infusion of ropivacaine resulted in signs of depression of conductivity and contractility.

In pediatric patients, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during general anaesthesia. It should be noted that NAROPIN (ropivacaine hydrochloride) is not approved for use in pediatric patients.

Treatment

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 anaesthetic injection and during continuous infusion. At the first sign of change, oxygen should be administered. If signs of acute systemic toxicity appear, injection of the local anaesthetic should be immediately stopped.

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

If necessary, use drugs to control the convulsions. An anticonvulsant should be given intravenously if the convulsions do not stop spontaneously in 15-20 seconds. Thiopental 1–3 mg/kg intravenous will abort the convulsions rapidly. Alternatively, diazepam 0.1 mg/kg intravenous may be used, although its action will be slow. Both these drugs, however, depress the central nervous system, respiratory and cardiac function, add to postictal depression, and may result in apnoea. Prolonged convulsions may jeopardize the patient's ventilation and oxygenation. If so, injection of a muscle relaxant such as succinylcholine (1 mg/kg) will stop the muscle convulsions rapidly, so that ventilation and oxygenation can be controlled. Endo-tracheal intubation must be considered in such situations.

If cardiovascular depression is evident (hypotension, bradycardia), it should be managed according to the patient condition and standard of anaesthetic care. Should circulatory arrest occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

Should cardiac arrest occur, prolonged resuscitative efforts may be required to improve the likelihood of a successful outcome.

Clinical data from patients experiencing local anaesthetic-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 anaesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

The supine position is dangerous in pregnant women at term because of aorto-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.

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 central nervous system symptoms (muscle twitching) were noted.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

Table 2 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Parenteral	Sterile isontonic solution 2 mg/mL, 5 mg/mL and 10 mg/mL ropivacaine hydrochloride	Sodium chloride, sodium hydroxide and/or hydrochloric acid (to adjust pH to 4 - 6), and water for injection

Description

NAROPIN 2 mg/mL for infusion (infiltration, nerve block and epidural) is available in a 100 and 200 mL Polybag (polypropylene infusion bag), packed in a sterile blister pack.

NAROPIN for injection (infiltration, nerve block and epidural) is available in 5 mg/mL (20 mL) and 10 mg/mL (10 and 20 mL) Polyamp (polypropylene ampoules suitable for Luer lock and Luer fit syringes),

packed in a sterile blister pack.

7 Warnings and Precautions

See 3 Serious Warnings and Precautions Box

General

Caesarean section: The 5 mg/mL NAROPIN solution in doses up to 150 mg is recommended. The 10 mg/mL solution should not be used for this indication. Historically, pregnant patients were reported to have a high risk for cardiac arrhythmias, cardiac/circulatory arrest and death when 0.75% bupivacaine (another member of the amino amide class of local anaesthetics) was inadvertently rapidly injected intravenously.

Reports of Irreversible Chondrolysis with Intra-articular Infusions of Local Anaesthetics Following Surgery: Intra-articular infusions of local anaesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of irreversible chondrolysis in patients receiving such infusions. The majority of reported cases of irreversible chondrolysis have involved the shoulder joint; cases of gleno-humeral irreversible chondrolysis have been described in pediatric and adult patients following intra-articular infusions of local anaesthetics with and without epinephrine for periods of 48 to 72 hours. The time of onset of symptoms, such as joint pain, stiffness and loss of motion can be variable, but may begin as early as the 2nd month after surgery. Currently, there is no effective treatment for irreversible chondrolysis; patients who experienced irreversible chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement. **NAROPIN should not be used for post-operative intra-articular infusion** (see 4 Dosage and Administration).

Major Peripheral Nerve Blocks: Major peripheral nerve blocks may imply the administration of a large volume of local anaesthetic in highly vascularized areas, often close to large vessels where there is increased risk of intravascular injection and/or rapid systemic absorption, which can lead to high plasma concentrations and serious adverse reactions (see 8 Adverse Reactions).

Inflammation and Sepsis: Local anaesthetic procedures should be performed with care in inflamed regions. Injections should not be performed through inflamed tissue nor when there is sepsis at or near the injection site.

Use with Other Local Anaesthetics: NAROPIN should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, since the toxic effects are additive (see 9 Drug Interactions).

Use in High-Risk Populations: Local anaesthetics should be used with caution in patients in poor general condition due to advanced age, debilitation, or other compromising factors such as partial or complete heart conduction block, advanced liver disease, or severe renal dysfunction (see 4 Dosage and Administration).

Use in Patients Treated with Class III Antiarrhythmic Drugs: Patients treated with class III antiarrhythmic drugs (e.g., amiodarone) should be under close surveillance and ECG monitoring, since

cardiac effects may be additive (see 9 Drug Interactions).

Epidural Anaesthesia and Analgesia

A well-known risk of epidural anaesthesia is unintentional subarachnoid injection of the local anaesthetic. Two clinical studies have been performed to verify the safety of NAROPIN. Doses of 15 and 22.5 mg in a 3 mL volume injected into the subarachnoid space were selected to be representative of an incremental epidural volume that could be unintentionally injected. The 15 and 22.5 mg doses injected resulted in sensory block levels as high as T5 and T4, respectively. Sensory block 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 15 and 22.5 mg doses (in 3 mL volume) did not produce any serious adverse events when spinal anaesthesia was achieved.

Epidural anaesthesia or analgesia may lead to hypotension and bradycardia which should be managed according to the patient condition and standard of anaesthetic care.

During epidural administration, it is recommended that a test dose of a local anaesthetic with a fast onset of action be administered initially. The patient should be monitored for central nervous system and cardiovascular toxicity, as well as for signs of unintended intrathecal administration, before proceeding. When clinical conditions permit, test doses of local anaesthetic solutions which contain epinephrine should be considered because circulatory changes compatible with epinephrine may also serve as a warning sign of unintended 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 rate should be continuously monitored. 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 anaesthetic such as lidocaine (30-40 mg) 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.

During epidural administration, ropivacaine should be administered in incremental doses of 3 to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or subarachnoid injection. Frequent aspirations for blood or cerebrospinal fluid (where applicable, i.e. when using a “continuous” intermittent catheter technique) should be performed before and during each supplemental injection because plastic tubing in the epidural space can migrate into a blood vessel or through the dura. A negative aspiration, however, does not ensure against an intravascular or intrathecal injection.

Cardiovascular

There have been rare reports of cardiac arrest during the use of NAROPIN for epidural anaesthesia or peripheral nerve blockade, especially after unintentional accidental intravascular administration in patients with concomitant heart disease (see 3 Serious Warnings and Precautions Box).

Local anaesthetics should be used with caution in patients with impaired cardiovascular function who may be less able to compensate for functional changes associated with prolongation of AV conduction produced by these drugs. Hypotension, hypovolemia, or partial or complete heart block represent risk factors.

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Ear/Nose/Throat

Small doses of local anaesthetics injected into the head and neck area, including dental and stellate ganglion blocks, may produce adverse reactions as a result of inadvertent intra-arterial injection and subsequent retrograde flow to the cerebral circulation. These adverse reactions may be similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression, and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. 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 4 Dosage and Administration).

Hematologic

NAROPIN is possibly porphyrinogen and should only be prescribed to patients with acute porphyria when no safer alternative is available. Appropriate precautions should be taken in the case of vulnerable patients.

Hepatic/Biliary/Pancreatic

Because amide-type local anaesthetics such as ropivacaine 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 anaesthetics normally, are at an increased risk of developing toxic plasma concentrations (see 4 Dosage and Administration, and 7 Warnings and Precautions, General, Use in High-Risk Populations).

Monitoring and Laboratory Tests

Following epidural administration, high sympathetic blockade or cranial spread of local anaesthetic especially in pregnant women may occasionally result in Horner's syndrome characterised by miosis, ptosis, and anhidrosis. In most cases, spontaneous resolution occurs upon discontinuation of treatment, but close supervision of patients undergoing epidural anaesthesia is recommended in order to address the potential risk of cardiorespiratory collapse due to a high sympathetic block

Neurologic

Psychomotor effects: Local anaesthetics may have a dose-dependent effect on mental function and coordination, causing temporary impairment of locomotion and alertness, even in the absence of overt central nervous system toxicity.

Ophthalmologic

Solutions of NAROPIN should not be used for the production of retrobulbar block due to insufficient data to support such use.

Until appropriate experience is gained, the use of NAROPIN for such surgery is not recommended.

Perioperative Considerations

- It is essential that aspiration for blood and cerebrospinal fluid be done prior to injecting any local anaesthetic, both for 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.

- Prior to receiving major blocks, the general condition of the patient should be optimized and have intravenous fluids running via an indwelling catheter to assure a functioning intravenous pathway.

- The healthcare professional responsible should take the necessary precautions to avoid intravascular injection (see 4 Dosage and Administration) and be trained, and familiar with, the diagnosis and treatment of side effects, systemic toxicity, and other complications.

- The lowest dosage of local anaesthetics that results in effective anaesthesia should be used. Injections should be made slowly and incrementally. When a continuous catheter technique is used, syringe aspirations should be performed before and during each supplemental injection.

- If blood is aspirated, relocate the needle. Inadvertent intravascular injection may cause serious consequences.

- Absorption is more rapid when injections are made into highly vascular tissues.

- Administration of higher than recommended doses of NAROPIN to achieve greater motor blockade or increased duration of sensory blockade may pose a particular risk in the event that an inadvertent intravascular injection occurs. In epidural administration, the procedure should be discontinued and re-initiated if the subarachnoid space has been entered, as shown by aspiration of spinal fluid.

Careful and constant monitoring of cardiovascular and respiratory vital signs (adequacy of ventilation) and the patient's state of consciousness should be performed during the anaesthetic procedure. It should be kept in mind at such times that restlessness, anxiety, incoherent speech, lightheadedness, 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.

Ropivacaine plasma concentrations may approach the threshold for central nervous system toxicity after the administration of 300 mg of ropivacaine for brachial plexus block. Caution should be exercised when using the 300 mg dose.

Renal

Local anaesthetics should be used with caution in patients in poor general condition due to severe renal dysfunction (see 4 Dosage and Administration).

Normally there is no need to modify the dose of NAROPIN when used for single dose or short-term treatment in patients with impaired renal function. Acidosis and reduced plasma protein concentration, frequently seen in patients with chronic renal failure, may increase the risk of systemic toxicity (see 10.3 Pharmacokinetics).

Reproductive Health

See 7.1.1 Pregnancy, and 16 Non-Clinical Toxicology

- **Fertility**

  No data are available.

7.1 Special Populations

7.1.1 Pregnancy

Reproduction studies have been performed in rats and rabbits.

No effects on fertility and general reproductive performance were seen in rats over two generations. At the highest dose level, increased pup loss was seen during the first three days post partum, which was considered to be secondary to impaired maternal care of the newborn, due to maternal toxicity.

Teratogenicity studies in rats and rabbits did not show evidence of any adverse effects of ropivacaine on organogenesis or early fetal development. There were no treatment-related effects on late fetal development, parturition, lactation, neonatal viability or growth of the offspring in a perinatal and postnatal study in rats using the maximum tolerated dose.

An additional perinatal and postnatal study in rats, in which ropivacaine was compared with bupivacaine, showed that maternal toxicity was observed at much lower dose levels and at lower unbound plasma concentrations of bupivacaine than of ropivacaine.

There are no clinical studies in preterm pregnant women on the effects of ropivacaine on the developing fetus. Ropivacaine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The use of ropivacaine at term for obstetric anaesthesia or analgesia is well documented.

Labour and Delivery: Local anaesthetics, including NAROPIN, rapidly cross the placenta, and when used for an epidural block, can cause varying degrees of maternal, fetal and neonatal toxicity. 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 epidural analgesia with NAROPIN for obstetrical pain relief. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. Lowered fetal heart rate causing fetal bradycardia has also been observed after NAROPIN administration. The fetal heart rate should be monitored continuously, and electronic fetal monitoring is highly advisable.

It is extremely important to avoid aorto-caval compression by the gravid uterus during administration of regional block to parturients. The patient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels be accomplished.

7.1.2 Breastfeeding

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. Caution should be exercised when NAROPIN is administered to a breast-feeding woman. Assuming that the milk/plasma concentration ratio in humans is of the same order, the total ropivacaine dose to which the baby is exposed by breast-feeding is far lower than by exposure in utero in pregnant women at term.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of NAROPIN have not been investigated in pediatric patients. In the pediatric population, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during general anaesthesia (see 5 Overdosage). NAROPIN is not indicated for use in patients below the age of 18 years.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Elderly patients should be given reduced doses of ropivacaine, commensurate with their age and physical condition (see 4 Dosage and Administration). The risk of hypotension and bradycardia in patients receiving epidural anaesthesia with NAROPIN increases in an age-dependent manner (see Table 7 in 8 Adverse Reactions).

There have been rare reports of cardiac arrest during the use of NAROPIN for epidural anaesthesia or peripheral nerve blockade, especially after unintentional accidental intravascular administration in elderly patients. In some instances, resuscitation has been difficult. Should cardiac arrest occur, prolonged resuscitative efforts may be required to improve the likelihood of a successful outcome.

8 Adverse Reactions

8.1 Adverse Reaction Overview

Reactions to NAROPIN (ropivacaine hydrochloride) are characteristic of those associated with other long-acting local anaesthetics of the amide type.

Adverse reactions to local anaesthetics are very rare in the absence of overdose or inadvertent intravascular injection. The effects of systemic overdose and unintentional intravascular injections can be serious, but should be distinguished from the physiological effects of the nerve block itself e.g., a decrease in blood pressure, bradycardia, urinary retention after epidural and intrathecal block, and events caused directly by needle puncture (e.g., spinal haematoma, postdural puncture, headache), or

indirectly by introduction of micro-organisms (e.g., meningitis and epidural abscess).

Acute systemic toxicity from local anaesthetics is generally dose-related and due to high plasma levels, which may result from overdosage (see 5 Overdosage), rapid absorption from the injection site, diminished tolerance, or from inadvertent intravascular injection. Most commonly, the acute adverse experiences originate from the central nervous and cardiovascular systems

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In clinical trials, the great majority of adverse events reported with ropivacaine were related to the expected effects of the block and to the clinical situation, rather than reactions to the drug. When all clinical studies were pooled (total n=3056), hypotension and nausea were registered in 41.2% (n=1259) and 28.4% (n=867) of the patients, respectively. Similar incidences were reported for bupivacaine in the double-blind comparisons.

Table 3 - Adverse Events Reported in ≥ 1% of Adult Patients Receiving Regional or Local Anaesthesia (Surgery, Labour, Caesarean Section, Peripheral Nerve Block, Local Infiltration and Post-Operative Pain Management)

Adverse Reaction	Total Number of Patients=2867							
	2 mg/mL		5 mg/mL		7.5 mg/mL		10 mg/mL	
	Total n=1360		Total n=740		Total n=540		Total n=222	
	n	%	n	%	n	%	n	%
hypotension	641	47.1	224	30.1	174	32.2	116	52.3
nausea	550	40.4	84	11.3	98	18.1	41	18.5
fever	281	20.7	11	1.5	6	1.1	6	2.7
vomiting	272	20	41	5.5	43	8	16	7.2
postoperative complications	204	15	21	2.8	3	0.6	3	1.4
anaemia	188	13.8	4	0.5	1	0.2	1	0.5
bradycardia	140	10.3	48	6.4	82	15.2	35	15.8
pain	140	10.3	42	5.6	15	2.8	2	0.9
oliguria	139	10.2						
dizziness	136	10	20	2.7	11	2	4	1.8
pruritus	123	9	10	1.3	16	3	2	0.9
hypertension	113	8.3	4	0.5	3	0.6		
unexpected therapeutic effect	108	7.9						
paraesthesia	107	7.9	51	6.8	14	2.6	3	1.4
hypoxia	86	6.3			2	0.4		
rigors (chills)	84	6.2	11	1.5	10	1.9	12	5.4
hypokalaemia	79	5.8	2	0.3				
headache	74	5.4	21	2.8	30	5.6	18	8.1
back pain	74	5.4	31	4.2	33	6.1	24	10.8
hypoproteinaemia	74	5.4						

Table 3 - Adverse Events Reported in ≥ 1% of Adult Patients Receiving Regional or Local Anaesthesia (Surgery, Labour, Caesarean Section, Peripheral Nerve Block, Local Infiltration and Post-Operative Pain Management)

Adverse Reaction	Total Number of Patients=2867							
	2 mg/mL		5 mg/mL		7.5 mg/mL		10 mg/mL	
	Total n=1360		Total n=740		Total n=540		Total n=222	
	n	%	n	%	n	%	n	%
diarrhoea	66	4.9	1	0.1	1	0.2	1	0.5
bradycardia fetal	66	4.9	2	0.3				
haematuria	63	4.6					2	0.9
urinary retention	62	4.6	7	0.9	8	1.5	5	2.3
hypothermia	62	4.6	1	0.1				
tachycardia	60	4.4	7	0.9			1	0.5
constipation	59	4.3	1	0.1	1	0.2		
abdominal pain	59	4.3	8	1.1				
urinary tract infection	48	3.5	1	0.1				
creatine phosphokinase increased	46	3.4						
hypoaesthesia	45	3.3	7	0.9	6	1.1	5	2.3
leukocytosis	44	3.2						
dyspepsia	42	3.1	1	0.1				
hypocalcaemia	41	3						
urine abnormal	40	2.9						
chest pain	39	2.9	4	0.5	3	0.6	1	0.5
anxiety	36	2.6	7	0.9	1	0.2	1	0.5
dyspnoea	35	2.6	3	0.4	1	0.2	2	0.9
hypotension postural	34	2.5						
abdomen enlarged	34	2.5	1	0.1				
oedema peripheral	33	2.4			3	0.6		
phosphatase alkaline increased	29	2.1						
injection site reaction	28	2.1			1	0.2		
insomnia	27	2						
thrombocytopenia	27	2						
infection	27	2			6	1.1	1	0.5
pleural effusion	26	1.9						
thrombocythaemia	26	1.9						
rash	25	1.8	4	0.5	3	0.6		
SGOT increased	25	1.8						
pyuria	25	1.8						
confusion	24	1.8	2	0.3	1	0.2		
faecal incontinence	24	1.8						
hyperglycaemia	23	1.7						
arthralgia	22	1.6	4	0.5			1	0.5
atelectasis	22	1.6						
bronchospasm	21	1.5	1	0.1				
rales	21	1.5						

Table 3 - Adverse Events Reported in ≥ 1% of Adult Patients Receiving Regional or Local Anaesthesia (Surgery, Labour, Caesarean Section, Peripheral Nerve Block, Local Infiltration and Post-Operative Pain Management)

Adverse Reaction	Total Number of Patients=2867							
	2 mg/mL		5 mg/mL		7.5 mg/mL		10 mg/mL	
	Total n=1360		Total n=740		Total n=540		Total n=222	
	n	%	n	%	n	%	n	%
albuminuria	20	1.5						
progression of labour poor/failed	20	1.5						
BUN decreased	19	1.4						
sweating increased	18	1.3			2	0.4	1	0.5
urinary incontinence	18	1.3	4	0.5	4	0.7	1	0.5
agitation	18	1.3			1	0.2		
somnolence	18	1.3			3	0.6		
SGPT increased	18	1.3			1	0.2		
coughing	18	1.3						
respiratory disorder	18	1.3						
respiratory insufficiency	18	1.3						
paresis	17	1.3	1	0.1				
injection site inflammation	16	1.2						
prothrombin decreased	16	1.2						
tremor	15	1.1	5	0.7	1	0.2	2	0.9
purpura	15	1.1	3	0.4			1	0.5
application site reaction	14	1						
myalgia	14	1	1	0.1				
hepatic function abnormal	14	1						
arrhythmia	14	1			1	0.2	1	0.5
micturition disorder	14	1			1	0.2	1	0.5
dysuria	8	0.6	2	0.3	2	0.4	3	1.4
jaundice neonatal	3	0.2	9	1.2				

Table 4A - Adverse Events Reported in ≥ 1% of Women who Received NAROPIN 5 mg/mL During Caesarean Section

Adverse Reaction	Total Number of Patients=173*	
	n	%
hypotension	101	58.4
paraesthesia	44	25.4
pain	29	16.8
nausea	27	15.6
vomiting	10	5.8
dizziness	7	4
anxiety	7	4
abdominal pain	7	4
pruritus	5	2.9
bradycardia	5	2.9
back pain	5	2.9
dyskinesia	4	2.3
headache	4	2.3
tachycardia	4	2.3
hypoaesthesia	3	1.7
tremor	2	1.2
anaemia	2	1.2
rigors (chills)	2	1.2
postoperative complications	2	1.2
postpartum haemorrhage	2	1.2

*some patients experienced more than one adverse event

Table 4B - Adverse Events Reported in ≥ 1% of Fetuses or Neonates of Mothers who Received NAROPIN 5 mg/mL During Caesarean Section

Adverse Reaction	Total Number of Patients=173*	
	n	%
jaundice neonatal	9	5.2
tachypnoea neonatal	6	3.5
respiratory disorder neonatal	3	1.7
bradycardia fetal	2	1.2

*some patients experienced more than one adverse event.

Table 4C - Adverse Events Reported in ≥ 1% of Women who Received NAROPIN 2 mg/mL During Labour

Adverse Reaction	Total Number of Patients=231*	
	n	%
hypotension	35	15.2
progression of labour poor/failed	20	8.7
paraesthesia	15	6.5
fever	15	6.5
back pain	13	5.6

Adverse Reaction	Total Number of Patients=231*	
	n	%
nausea	9	3.9
pain	7	3
vomiting	6	2.6
rigors (chills)	6	2.6
bradycardia	5	2.2
urinary tract infection	4	1.7
dystocia	4	1.7
urinary retention	3	1.3
tachycardia	3	1.3
jaundice	3	1.3

*some patients experienced more than one adverse event.

Table 4D - Adverse Events Reported in ≥ 1% of Fetuses or Neonates of Mothers Who Received NAROPIN 2 mg/mL During Labour

Adverse Reaction	Total Number of Patients=231*	
	n	%
bradycardia fetal	66	28.6
fetal distress	10	4.3
tachycardia fetal	7	3
fever neonatal	6	2.6
vomiting neonatal	4	1.7
apgar score low	4	1.7
jaundice neonatal	3	1.3
hypoglycaemia neonatal	3	1.3
neonatal complication (Not Other Specified)	3	1.3
tachypnoea neonatal	3	1.3
respiratory disorder neonatal	3	1.3

*some patients experienced more than one adverse event.

Table 5 - Common Events (Epidural Administration)

Adverse Reaction	NAROPIN					
	5 mg/mLTotal n=256		7.5 mg/mLTotal n=297		10 mg/mLTotal n=207	
	n	(%)	n	(%)	n	(%)
hypotension	99	(38.7)	146	(49.2)	113	(54.6)
nausea	34	(13.3)	68	(22.9)	-	-
bradycardia	29	(11.3)	58	(19.5)	40	(19.3)
back pain	18	(7)	23	(7.7)	34	(16.4)
vomiting	18	(7)	33	(11.1)	23	(11.1)
headache	12	(4.7)	20	(6.7)	16	(7.7)
fever	8	(3.1)	5	(1.7)	18	(8.7)

Table 6 - Most common adverse events by gender (epidural administration). Total n: female=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)	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)	3	(0.8)
pruritus	16	(4)	1	(0.3)

Table 7 - Incidence of Hypotension in Relation to Age (Epidural Administration) Total N: NAROPIN=760

Age	NAROPIN					
	5 mg/mL		7.5 mg/mL		10 mg/mL	
	n	(%)	n	(%)	n	(%)
< 65	68	(32.2)	99	(43.2)	87	(51.5)
≥ 65	31	(68.9)	47	(69.1)	26	(68.4)

Central Nervous System: 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 anaesthetics varies with the procedure used and the total dose administered.

For a detailed description of Central Nervous System toxicity, please see 5 Overdosage.

Cardiovascular System: 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 cardiac arrest. Reactions due to systemic absorption may be either slow or rapid in onset.

Cardiovascular collapse and cardiac arrest can occur rapidly (see 5 Overdosage, and 7 Warnings and Precautions, General).

Allergic: Allergic type reactions are rare and may occur as a result of sensitivity to local anaesthetics of the amide-type. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic oedema (including laryngeal oedema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and in the most severe instances, anaphylactic shock.

Neurologic: The incidence of adverse neurologic reactions may be related to the total dose of local anaesthetic administered but is also dependent upon the particular drug used, the route of administration and the physical status of the patient. Neuropathy and spinal cord dysfunction (e.g., anterior spinal artery syndrome, arachnoiditis, cauda equina syndrome), have been associated with regional anaesthesia. Neurological effects may be related to local anaesthetic techniques, with or without a contribution from the drug.

During epidural block, occasional unintentional penetration of the subarachnoid space by the catheter or needle may occur. Neurologic effects following unintentional subarachnoid administration during epidural anaesthesia may include spinal block of varying magnitude (including total or high spinal block) and hypotension secondary to spinal block. A high spinal block is characterized by limb paralysis, loss of consciousness, respiratory paralysis and bradycardia.

Other neurological effects following unintentional subarachnoid administration during epidural anaesthesia may include persistent anaesthesia, paraesthesia, weakness, paralysis of the extremities and loss of sphincter control, all of which may have slow, incomplete or no recovery. Urinary retention, loss of bladder and bowel control (faecal and urinary incontinence), and loss of perineal sensation and sexual functions are extremely rare but possible neurotoxic complications. Headache, septic meningitis, meningismus, slowing of labour, increased incidence of forceps delivery, or cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid have been reported.

Elevation of Body Temperature: Epidural infusion of NAROPIN has, in some cases, been associated with transient elevations in body temperature to >38.5°C. This has occurred more frequently at doses greater than 16 mg/hour. The pyrexia seen in connection with postoperative epidural infusion of ropivacaine is similar to that seen with bupivacaine. Body temperature is not affected by systemic concentrations of ropivacaine.

9 Drug Interactions

9.3 Drug-Behaviour Interactions

Besides the direct anaesthetic effect, local anaesthetics may have a very mild effect on mental function and coordination even in the absence of overt central nervous system toxicity and may temporarily impair locomotion and alertness.

9.4 Drug-Drug Interactions

The drugs listed are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Local anaesthetics and agents structurally related to amide-type local anaesthetics
NAROPIN (ropivacaine hydrochloride) should be used with caution in patients receiving other amide-type local anaesthetics such as lidocaine, bupivacaine, mepivacaine and prilocaine since toxic effects are additive.

Antiarrhythmic Drugs
NAROPIN should be used with caution with structurally related agents such as the antiarrhythmics procainamide, disopyramide, tocainide, mexiletine and flecainide.

Class III Antiarrhythmic drugs: Specific interactions studies with ropivacaine and class III anti-arrhythmic drugs (e.g., amiodarone) have not been performed. Caution is advised when using Class III antiarrhythmic drugs concomitantly with ropivacaine due to potential pharmacodynamic or pharmacokinetic interactions, or both (see 7 Warnings and Precautions, General). Patients treated with class III antiarrhythmic drugs should be under close surveillance and ECG monitoring since cardiac effects may be additive.

Sedatives
If sedatives are employed to reduce patient apprehension, they should be used in reduced doses, since local anaesthetic agents, like sedatives, are central nervous system depressants which in combination may have an additive effect.

Strong Inhibitors of P4501A2
In vitro studies indicate that the cytochrome P4501A2 is involved in the formation of 3-hydroxy ropivacaine, the major metabolite.

Fluvoxamine and Enoxacin: In healthy volunteers, the plasma clearance of ropivacaine was reduced by up to 77% during co-administration of fluvoxamine, a selective and potent P4501A2 inhibitor. Thus, strong inhibitors of cytochrome P4501A2, such as fluvoxamine, and enoxacin, given concomitantly during repeated administration of NAROPIN, can interact with NAROPIN. Prolonged administration should be avoided in patients treated with such strong inhibitors of P4501A2.

Theophylline and Imipramine: Interactions with drugs known to be metabolized by P4501A2 via competitive inhibition, such as theophylline and imipramine may occur, but should be of less importance.

9.5 Drug-Food Interactions

Interactions of ropivacaine with food have not been established.

9.6 Drug-Herb Interactions

Interactions of ropivacaine with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions of ropivacaine with laboratory tests have not been established.

10 Clinical Pharmacology

10.1 Mechanism of Action

NAROPIN (ropivacaine hydrochloride), a local anaesthetic of the amino amide class, is supplied as the pure S-(-)-enantiomer.

NAROPIN has both local anaesthetic and analgesic effects. At high doses, surgical anaesthesia is achieved. At lower doses, NAROPIN produces sensory block (analgesia) with limited and non-progressive motor block

NAROPIN, like other local anaesthetics, causes reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the cell membrane of the nerve fibres.

Onset and Duration of Action
The duration of action of local anaesthetics depends on the injection site, the route of administration, and the concentration and volume of the drug. The duration and intensity of ropivacaine block are not improved by the addition of epinephrine. After epidural infusion of ropivacaine, the spread of sensory block and the degree of motor block, as well as their subsequent regression, are dose dependent.

10.2 Pharmacodynamics

Ropivacaine, like other local anaesthetics, can also have effects on the central nervous and cardiovascular systems. If excessive amounts of drug reach the systemic circulation, symptoms and signs of central nervous system toxicity and cardiotoxicity may appear.

Signs and symptoms of central nervous system toxicity (see 5 Overdosage) generally occur at lower plasma concentrations than do those of cardiotoxicity. Following systemic absorption, local anaesthetics 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, leading ultimately to respiratory arrest. However, the local anaesthetics have a primary depressant effect on the medulla and on higher centres. The depressed stage may occur without a prior excited stage. High blood concentrations of local anaesthetics resulting from systemic absorption or intravascular injection can depress cardiac conduction and excitability. At toxic levels, atrioventricular block, ventricular arrhythmias, cardiac arrest, and death are possibilities.

Indirect cardiovascular effects (hypotension, bradycardia) may occur after epidural administration, depending on the extent of the concomitant sympathetic block.

In two clinical pharmacology studies (total N=24) ropivacaine and bupivacaine were infused (10 mg/min) in human volunteers until the appearance of central nervous system 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.

Animal
Ropivacaine has been demonstrated to produce topical, infiltration, epidural, and brachial plexus anaesthesia in a range of animal models with potency and pharmacodynamic characteristics similar to those of bupivacaine. Like bupivacaine, ropivacaine is also capable of inducing convulsions and hemodynamic changes when administered intravenously in large doses.

The convulsant doses of intravenously administered ropivacaine and bupivacaine were similar in mice, rats, and dogs. In sheep, ropivacaine was less proconvulsant than was bupivacaine when the drugs were administered by intravenous infusion. Both ropivacaine and bupivacaine exhibited considerably more proconvulsant activity than did lidocaine.

The cardiovascular effects of convulsant and superconvulsant doses of ropivacaine and bupivacaine has been assessed in unanaesthetized and anaesthetized animals. In unanaesthetized rats, convulsant doses of intravenous ropivacaine caused a 50% increase in QRS duration while bupivacaine resulted in a 100% increase. In unanaesthetized dogs, 2/6 animals which received intravenous ropivacaine at two times the convulsant dose experienced ventricular arrhythmias, while the incidence for bupivacaine was 5/6 animals.

Cardiovascular changes were similar for both drugs in pentobarbital anaesthetized pigs administered maximum intravenous doses or ropivacaine (4 mg/kg) and bupivacaine (3 mg/kg).

In a blinded study of sheep, the dose of ropivacaine required to produce cardiotoxicity (circulatory collapse) was consistently greater than that for bupivacaine (Table 8).

Ropivacaine and other class-related local anaesthetics caused convulsions at lower doses in pregnant ewes compared to non-pregnant ewes, but pregnancy did not increase the sensitivity of ewes to other serious manifestations of systemic toxicity (e.g., hypotension, apnoea, and circulatory collapse).

Table 8 - Dose Required to Produce Convulsions and Circulatory Collapse in Pregnant Sheep

	Intravenous Dose (mg/kg)			
	Convulsions		Circulatory Collapse	
	Non-Pregnant	Pregnant	Non-Pregnant	Pregnant
ropivacaine	6.1	7.5	11.6	12.9
bupivacaine	4.6	5	8.9	8.5

10.3 Pharmacokinetics

Absorption

The systemic concentration of local anaesthetics is dependent upon the total dose and the concentration administered, the route of administration, the patient's hemodynamic/ circulatory condition, and the vascularity of the injection site. Ropivacaine follows linear pharmacokinetics and the maximum plasma concentration is proportional to the dose.

Ropivacaine shows complete and biphasic absorption from the epidural space. The mean half-lives of the two phases are in the order of 14 min and 4 h. The slow absorption is the rate-limiting factor in the elimination of ropivacaine, which explains why the apparent elimination half-life is longer after epidural than after intravenous administration. Ropivacaine shows dose proportionality at epidural doses up to 250 mg and intravenous doses up to 80 mg.

Distribution

Following intravenous administration, the volume of distribution of ropivacaine is approximately 40 L. Ropivacaine is extensively bound to alpha1-acid glycoprotein in plasma with an unbound, i.e., pharmacologically active, fraction of about 6%. An increase in total plasma concentration during continuous epidural infusion has been observed in postoperative patients and is related to the postoperative increase of alpha1-acid glycoprotein. Variations in unbound concentration have been much less than in total plasma concentration.

Ropivacaine readily crosses the placenta and equilibrium, in regard to unbound concentration, is rapidly reached. The degree of plasma protein binding in the fetus is less than in the mother, which results in lower total plasma concentrations in the fetus than in the mother. The ratios of umbilical vein to maternal vein total and free concentrations are 0.31 and 0.74, respectively.

Metabolism

There is no evidence of in vivo racemization of ropivacaine. Ropivacaine is extensively metabolized in the liver predominantly to 3-hydroxy-ropivacaine by an aromatic hydroxylation process mediated by cytochrome P4501A2 and N-dealkylation to S-PPX mediated by CYP3A4. Conjugated and unconjugated 3-hydroxy-ropivacaine represent the major urinary metabolites. Urinary excretion of 4-hydroxy ropivacaine, N-dealkylated pipecoloxylidide (S-PPX) and both the 3-hydroxy and 4-hydroxy N-dealkylated metabolites account for less than 3% of the dose. An additional metabolite, 2-hydroxy-methyl-ropivacaine has been identified, but not quantified in urine. S-PPX and 3-hydroxy ropivacaine are the major metabolites excreted in the urine during epidural infusion. A total S-PPX concentration in

the plasma was about half that of total ropivacaine however, mean unbound concentrations of S-PPX were about 7 – 9 times higher than that of unbound ropivacaine following continuous epidural infusion up to 72 hours. The threshold for central nervous system toxicity in rats due to unbound plasma concentrations of S-PPX is approximately 12 times higher than that of unbound ropivacaine. S-PPX, 3-hydroxy ropivacaine, and 4-hydroxy ropivacaine have a pharmacological activity in animal models less than that of ropivacaine.

Impaired renal function has little or no influence on unchanged ropivacaine pharmacokinetics. The renal clearance of S-PPX is significantly correlated with creatinine clearance. A lack of correlation between total exposure, expressed as AUC, with creatinine clearance indicates that the total clearance of S-PPX includes a non-renal elimination in addition to renal excretion. Some patients with impaired renal function may show an increased exposure to S-PPX resulting from a low non-renal clearance. The relevance to humans of this increased exposure to S-PPX is unknown at this time.

Elimination

After intravascular administration, 86% of the total dose of ropivacaine is excreted in the urine of which approximately 1% is the parent compound and 36% is 3-hydroxy- ropivacaine. Ropivacaine has a mean total plasma clearance in the order of 440 mL/min, an unbound plasma clearance of 8 L/min, a renal clearance of 1 mL/min, and a volume of distribution at steady state of 47 L. Ropivacaine has an intermediate hepatic extraction ratio of about 0.4. The terminal elimination half-life is 1.6 to 1.8 hours after intravenous administration, 4.1-6.5 hours after epidural administration, and 5.7-8 hours after brachial plexus block. The total and unbound clearance of epidural ropivacaine at term in pregnancy (223-256 mL/min and 2.8-3.3 L/min, respectively), are lower than that observed in non-pregnant patients.

11 Storage, Stability, and Disposal

Store solutions at 15-25°C. Do not freeze. Store in carton prior to use

NAROPIN (ropivacaine hydrochloride) solutions are sterile, without preservative and are for single use only. Discard unused portion.

Due to the nature of the Polyamp and the Polybag systems, the containers must not be re-autoclaved

Part 2: Scientific Information

13 Pharmaceutical Information

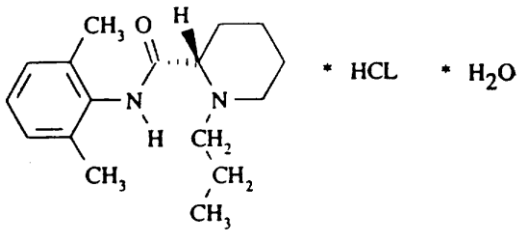
Drug Substance

Non-proprietary name of the drug substance(s): ropivacaine hydrochloride monohydrate

Chemical name: S-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate

Molecular formula and molecular mass: C17H26N2O.HCl.H2O, 328.89

Structure (for biologics)/Structural formula:



Physicochemical properties: Ropivacaine is a pure enantiomer. A white crystalline powder with a pKa of 8.1, solubility in water at 25ºC is 53.8 g/L and a distribution ratio of 141 (25°C n-octanol/phosphate buffer pH 7.4)

14 Clinical Trials

14.1 Clinical Trials by Indication

Epidural Administration in Surgery

The use of NAROPIN (ropivacaine hydrochloride) for epidural anaesthesia in general surgery was investigated in 25 clinical studies performed in 942 patients. NAROPIN was administered in doses ranging from 75 to 250 mg. The intensity and duration of sensory and motor block were dose dependent. At doses ranging from 100-200 mg, the median time to achieve a T10 sensory block was 10 (5-13) minutes, while the median duration of anaesthesia at this dermatome was 4 (3-5) hours. The median duration of motor block for 20 mL of a 5 mg/mL solution was 3 hours; 7.5 mg/mL, 4 hours; and 10 mg/mL, 5 hours.

Epidural Administration in Caesarean Section

Seven studies of epidural anaesthesia with NAROPIN have been performed in a total of 173 women undergoing Caesarean section. NAROPIN 5 mg/mL was administered at mean total doses ranging from 110 to 150 mg. The median onset of sensory block at T6 ranged from 11 to 26 minutes, while the median duration of sensory block at this dermatome ranged from 1.7 to 3.2 hours. The duration of motor block ranged from 1.4 to 2.9 hours. The quality of analgesia was considered to be satisfactory in 73-100% of patients, while the quality of muscle relaxation was rated as satisfactory in 100% of patients.

Major Nerve Block
Twelve studies (n=363) have been performed to investigate the efficacy of NAROPIN in a single instance of major nerve block, brachial plexus block. In studies in which the 5 mg/mL solution (total doses of 175-190 mg) was administered by the supraclavicular approach, anaesthesia at dermatomes T1 to C5 was achieved in 83-100% of patients. Following median onset times ranging from 10 to 25 minutes, the median duration of anaesthesia at these dermatomes ranged from 8 to 12 hours. The quality of brachial plexus block was rated as satisfactory in 91-100% of these patients.

Success rates were lower with axillary blocks than with supraclavicular blocks. In patients receiving 175-275 mg of NAROPIN 5 mg/mL by the axillary approach, satisfactory analgesia was achieved in 62-72% of patients. The frequency of anaesthesia at the nerves studied ranged from 52-90%. The median onset time ranged from 10-45 min with a median duration of anaesthesia in the range of 3.7 to 8.7 hours.

In studies in which NAROPIN 7.5 mg/mL was administered for the production of supraclavicular brachial plexus block (total dose 225 mg) analgesia was achieved in the nerves studied in 82-96% of patients and anaesthesia was achieved in 51-63% of patients. The median onset time of analgesia was 5 to 7 minutes, with a median duration of 11.4 to 14.4 hours. The median onset time of anaesthesia was 15 to 19 minutes, with a median duration of 8.5 to 11.1 hours. The quality of brachial plexus block (i.e., analgesia and muscle relaxation) was rated as satisfactory/excellent in 69-77% of patients.

In patients receiving NAROPIN 7.5 mg/mL (total dose 300 mg) by the axillary approach, analgesia was achieved in the nerves studied in 64-100% of patients and anaesthesia was achieved in 65-81% of patients (excluding the axillary nerve in which anaesthesia was achieved in 14% of patients). The median onset time of analgesia varied from 5 to 20 minutes, with a median duration of 11.4 to 13.2 hours (excluding the axillary nerve which had a duration of 5 to 6 hours). The median onset time of anaesthesia was 20 to 30 minutes, with a median duration of 8.4 to 10.8 hours (excluding the axillary nerve which had a duration of 2.4 hours). The quality of brachial plexus block was rated as satisfactory/excellent in 96-100% of patients.

Epidural Administration in Labour and Delivery
Nine studies have been performed to investigate the use of epidural NAROPIN for pain relief during labour in pregnant females with full term singleton fetuses in the vertex presentation. Loading doses of approximately 25 mg were administered as fractionated doses. In four clinical trials in which continuous infusions were administered, the total infusion dose ranged from 3-30 mg/h with median values of 22-25 mg/h. Infusion times up to 13 hours have been studied. In the remaining studies, supplementary analgesia was provided by up to 8 top up doses of NAROPIN at median doses ranging from 14-18 mg/hr. In these studies, the median values for the onset of pain relief after the main dose ranged from 9-18 min. Median upper spread of sensory block ranged from T5 to T10.

Epidural Administration in Postoperative Pain Management
Sixteen clinical trials (n=1049) have been performed to investigate the lumbar-thoracic epidural use of NAROPIN 2 mg/mL in postoperative pain management following orthopaedic or upper or lower abdominal surgery. All patients received epidural anaesthesia with NAROPIN 5, 7.5 or 10 mg/mL or general anaesthesia intraoperatively prior to the initiation of postoperative epidural infusion.

In studies investigating infusion times up to 21 hours, the infusion of NAROPIN at doses ranging from 10-30 mg/h was associated with decreases in pain scores and narcotic requirement. The frequency and intensity of motor block tended to decrease during the 21-hour period. Motor block was dose rate dependent. In two dose-controlled studies, infusion rates of 12-28 mg/h provided satisfactory analgesia (85-100% rated good or excellent) with relatively slight motor block. Sensory block was also dose rate-dependent and a decrease in spread was observed during the infusion period.

Two clinical studies have investigated the epidural infusion of NAROPIN 2 mg/mL (6-14 mL/h) for up to 72 hours of postoperative pain management following major abdominal surgery. Also included in this series, were study groups receiving epidural infusion of NAROPIN 2 mg/mL mixed with fentanyl 1-4 µg/mL at rates up to 28 mg/hour. NAROPIN admixed with or without fentanyl, provided good/excellent pain relief for 87-100% of patients treated for up to 72 hours. In both studies, after 24 hours, 87-92% of the patients were without measurable motor block. No motor block was reported thereafter in 97-100% of patients. Although the combination of NAROPIN and fentanyl provided improved pain relief, there were narcotic side effects and hospitalization was prolonged.

Infiltration
Pre- and postoperative wound infiltrations with NAROPIN for postoperative pain relief have been studied in six clinical trials. An additional study examined local infiltration with ropivacaine for operation upon benign nevi. In total, 308 patients were studied. In the wound infiltration studies, ropivacaine at doses of 100-200 mg resulted in lower pain scores and/or a decreased analgesia requirement in the immediate post-operative period in 3 of 4 studies which contained inactive control groups. In the study of nevus excision, doses of 5-20 mg were considered to provide adequate analgesia in the 30 patients studied.

16. Non-Clinical Toxicology

General toxicology

Single Dose Studies
Acute toxicity has been studied in mice and rats and besides death, the main signs observed were decreased motor activity, dyspnoea, piloerection, tremor, ataxia and clonic convulsions. These were all expected signs after administration of high doses of a local anaesthetic agent.

Table 9 - Toxicity After Single Administration of Ropivacaine to Mice and Rats

Species/Strain	Body Wt. (g)	No. Dose Groups	No. Animals/Group	Route of Administration	Estimated LD_{50} (mg/kg)
Mouse/NMRI	17-25	7	2-5	s.c.	>120
	15-21	5	2-5	s.c.	100
Mouse/NMRI	16-20	4	5	i.v.	14-20

Species/Strain	Body Wt. (g)	No. Dose Groups	No. Animals/Group	Route of Administration	Estimated LD_{50} (mg/kg)
	15-19	4	5	i.v.	28
Rat/Sprague Dawley	270-340	4	5	s.c.	58-69
	180-220	4	2-5	s.c.	76
Rat/Sprague Dawley	180-210	4	2-5	i.v.	9.9
	150-180	4	2-5	i.v.	12

s.c.: subcutaneous; i.v.: intravenous

Long-Term Multidose Studies

In a two-week dose finding study in rats, the maximum tolerated subcutaneous dose of ropivacaine was determined to be below 30 mg/kg when 7 of 12 animals at this dose experienced convulsions which were fatal in 3 cases. In the main study, rats were treated subcutaneously with 3.3, 9.9 or 26 mg/kg ropivacaine for 1 month. A single male at the highest dose level showed convulsions and cyanosis on one occasion. The clinical chemistry investigation showed a slight, but dose dependent, decrease in serum potassium concentration. However, all values were within the laboratory reference limits. The pathological investigation did not disclose any changes that were caused by treatment with ropivacaine.

In dogs, the maximum tolerated subcutaneous dose of ropivacaine was reported to be below 16 mg/kg after convulsions were observed in one of six animals at this dose level. In a later study, also performed in dogs, repeated daily administration of ropivacaine for 1 month at 3.3, 6.6 and 13 mg/kg, caused vomiting and tremor in all drug treated groups with females at the highest dose level being most affected. These signs are comparable with known actions of other local anaesthetics on the central nervous system at this dosage range. No clinical, chemical or pathologic changes that could be attributed to treatment were seen.

Local Tolerance

Single perineural or intraneural (intrafascicular) injection of ropivacaine 7.9 mg/mL in rats produced no evidence of neurotoxicity in any of the treated nerves. Neither was there any indication of a neurotoxic effect in dogs after single epidural or intrathecal injection of ropivacaine 7.9-10.6 mg/mL, or after continuous epidural infusion of ropivacaine 6 mg/mL for 5 days. The effects of ropivacaine on the spinal cord were also evaluated in rats after twice daily i.t. injections of 2.6, 5.3 or 11 mg/mL ropivacaine for two weeks. Assessment of the dose required to produce spinal anaesthesia did not change with time and, again, there was no evidence of neurotoxicity.

Continuous epidural infusion (up to 0.34 mg/kg) for 4 consecutive weeks of ropivacaine 4 mg/mL with or without fentanyl in Beagles produced no treatment-related neurological signs, other than paresis and paralysis which were considered to be consistent with the pharmacological actions of an epidurally administered local anaesthetic agent. Generally, these responses decreased during the latter half of the 4 week infusion period and disappeared on discontinuation of the infusion. The presence of fentanyl necessitated a step-up dosing procedure, but once the highest dose of ropivacaine had been achieved fentanyl did not change the response to the drug.

Genotoxicity
Weak mutagenic activity was found in the two mouse lymphoma tests performed. In the first test, weakly positive results were observed at the highest concentration of ropivacaine (890 mg/L) without metabolic activation and with metabolic activation in the 49-160 mg/L range. In the repeat test, in which a physiological medium was used, ropivacaine showed no mutagenic activity in the absence of activation despite achieving a two-fold increase in test compound concentration. With metabolic activation, a lower magnitude of mutagenic activity than in the first study was seen at concentrations of 70-210 mg/mL. No mutagenic activity was noted in any of the other in vitro systems or in vivo systems studied.

Reproductive and developmental toxicology
Ropivacaine did not affect fertility or general reproductive performance over two generations in rats at dose levels up to 23 mg/kg when administered subcutaneously to males for 9 weeks up until mating, and in females, for two weeks prior to mating and up to 42 days post coitus. An increased pup loss was observed during the first few days post parturition in the 23 mg/kg dose group, but this was considered secondary to impaired maternal care of the newborn. Pregnant rats given up to 26 mg/kg ropivacaine subcutaneously on days 6-15 of pregnancy showed no signs of adverse effects on organogenesis and early fetal development.

In a dose finding study, pregnant rabbits administered 16 or 21 mg/kg ropivacaine subcutaneously on days 6-18 of pregnancy experienced a reduction in motor activity, reduction in body weight gain and convulsions. The convulsions resulted in the death of 2 of 4 animals. Fetal weight gain was decreased. Thus, the highest dose level was reduced in the main teratology study. In this study, ropivacaine at doses of up to 13 mg/kg subcutaneously did not affect organogenesis and early fetal development.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

NAROPIN®

ropivacaine hydrochloride injection
ropivacaine hydrochloride for epidural infusion

This Patient Medication Information is written for the person who will be receiving **NAROPIN**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.
This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **NAROPIN**, talk to a healthcare professional.

Serious warnings and precautions box

- NAROPIN is for healthcare professional use only.
- Your healthcare professional will be trained in the management and care of local anaesthetics, such as NAROPIN. They will prepare and give you NAROPIN in a hospital setting with the adequate equipment for the proper management of unwanted side effects. They will also monitor your health throughout the treatment.

What NAROPIN is used for:

NAROPIN is used in adults to prevent or relieve pain to an area of the body. This can include before and after a surgery, during labour, or after a sudden injury.

How NAROPIN works:

NAROPIN belongs to a group of medicines known as local anaesthetics. They act by temporarily preventing the nerves around the injection site from transmitting sensations of pain, heat or cold. However, you may still experience sensations such as pressure and touch. In many cases, the nerves to the muscles in the area will also be blocked. This may cause temporary weakness or paralysis (loss of voluntary muscle function). Overall, this helps to prevent or relieve pain to an area of the body.

The ingredients in NAROPIN are:

Medicinal ingredient: ropivacaine hydrochloride.

Non-medicinal ingredients: sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), and water for injection.

NAROPIN comes in the following dosage form:

- Sterile isotonic solution in infusion bags; 2 mg / mL

- Sterile isotonic solution in ampoules; 5 mg / mL and 10 mg / mL

Do not use NAROPIN if:

- you are allergic to ropivacaine, other anaesthetics that end with "-caine, or any of the other ingredients in NAROPIN. If you are unsure, ask your healthcare professional.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive NAROPIN. Talk about any health conditions or problems you may have, including if you:

- are taking any other medications, including other local anaesthetics or medicines used to treat abnormal heartbeat and heart rhythms.
- have inflamed skin or a severe reaction to an infection (sepsis) at or near the proposed site of injection for NAROPIN.
- have a condition that causes weakness or frailty.
- are severely ill.
- have low blood pressure.
- have heart, blood vessel or blood circulation problems.
- have liver or kidney disease.
- have porphyria (an inherited or acquired disorder involved in making red blood pigment).
- are pregnant or planning to become pregnant. NAROPIN should only be used during pregnancy if your healthcare professional has decided that the potential benefits outweigh the potential risks to your unborn child.
- are breastfeeding or planning to breastfeed. NAROPIN can pass into your breast milk.

Other warnings you should know about:

NAROPIN may cause serious side effects, including:

- **Hypotension** (low blood pressure) or **Bradycardia** (low heart rhythm) when NAROPIN is administered into the space around the spinal cord (epidural). The risk of experiencing hypotension and bradycardia increases as you get older.

- **Cardiac arrest** (heart suddenly stops beating): This rarely occurred during the usual administration of NAROPIN, and occurred after its accidental administration into a blood vessel in patients with heart disease.

See the **Serious side effects and what to do about them** table for more information on this and other serious side effects.

Irreversible chondrolysis (permanent loss of cartilage in a joint): You may experience this side effect if NAROPIN is not administered as it should be. In most reported cases, the shoulder joint was affected. Symptoms included joint pain, stiffness and loss of motion, and began as early as 2 months after administration. Tell your healthcare professional **right away** if you experience these symptoms after surgery. You may require further therapeutic procedures or surgery.

Horner's syndrome (a rare neurological syndrome): You may experience this side effect when NAROPIN is administered into the space around the spinal cord (epidural). It usually goes away once your treatment with NAROPIN is discontinued. Tell your healthcare professional **right away** if you experience decreased size of the pupil of the eye, drooping eyelid, decreased sweating on the affected side of the face.

Driving and using machines: NAROPIN may temporarily interfere with your reactions and coordination. Before you do tasks that may require your attention, you should wait until you know how you react to your treatment.

Testing and monitoring: Your healthcare professional will regularly monitor your health throughout your treatment. This may include monitoring:

- how you react to your dose;
- your blood pressure, heart rate, heart rhythm, and heart and blood vessel functions;
- your breathing and lung function;
- your vision.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NAROPIN:

- antiarrhythmics, medicines used to treat abnormal heartbeat and heart rhythms (e.g., procainamide, disopyramide, flecainide, mexiletine, amiodarone)
- other local anaesthetics, medicines used to prevent pain during surgery (e.g., lidocaine, bupivacaine, mepivacaine, prilocaine)
- sedatives, medicines that can increase drowsiness
- antidepressants, medicines used to treat depression (e.g., fluvoxamine, imipramine)
- theophylline, used to treat asthma and other lung problems

How NAROPIN is given:

NAROPIN will be administered to you:

- by a healthcare professional in a healthcare setting.
- into the space around your spinal cord (epidural) or near a nerve or a group of nerves (block/infiltration). NAROPIN should not be given by any other route.
- slowly and gradually.

Your healthcare professional may administer a test dose at first before administering NAROPIN. The test dose will consist of a fast-acting local anaesthetic. This is to ensure you react well to this type of medication and to ensure the needle or catheter is properly placed

Usual dose:

NAROPIN will be administered by your healthcare professional. Your dose will depend on:

- your age and weight,

- your medical condition,
- how you respond to the treatment,
- if you take other medicines, and/or
- the type of surgery.

The lowest effective dose of NAROPIN will be used.

Overdose:

Your healthcare professional will monitor you for signs and symptoms of an overdose. If an overdose is suspected, your healthcare professional will act accordingly to manage your side effects.

Symptoms of an overdose with NAROPIN include:

- feeling dizzy or light-headed
- numbness of the lips and around the mouth
- numbness of the tongue
- hearing problems
- tingling in the ears
- problems with your vision
- problems with speech
- twitching muscles or tremors (shaking)
- seizures (fits)
- loss of consciousness
- change in heart rhythm
- low blood pressure
- cardiac arrest (heart suddenly stops beating)

If you notice any of these symptoms, tell your healthcare professional **right away**.

If you think you, or a person you are caring for, have been given too much NAROPIN, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Possible side effects from using NAROPIN:

These are not all the possible side effects you may have when taking NAROPIN. If you experience any side effects not listed here, tell your healthcare professional.

Side effects with NAROPIN include:

- Back pain
- Headache
- Itching
- Nausea or vomiting

- Reactions at the site of injection (e.g., bruising, pain, redness, burning sensation)
- Sensation of tingling, numbness or burning in the skin
- Feeling dizzy or anxious
- Low body temperature
- Bladder infection

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Very common			
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		✓	
Common			
Arrhythmias (abnormal heart rhythms): rapid (tachycardia), slow (bradycardia), or irregular heartbeat		✓	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations		✓	
Urinary retention (inability to pass urine or to empty the bladder): hard to start the flow of urine, slow urine stream, or unable to completely empty your bladder when urinating		✓	
High body temperature (fever) or chills		✓	
Uncommon			
Fainting		✓	
Difficulty breathing		✓	
Toxicity symptoms: convulsions, seizures, feeling dizzy or light-headed, numbness of the lips and around the mouth, numbness of		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
the tongue, hearing problems, vision problems, problems with speech, stiff muscles, and trembling			
Numbness		✓	
Nerve problems: back pain, loss or impairment of motor and sensory function, paralysis, decreased sensitivity or feeling in the skin, or other sensory disturbances		✓	
Rare			
Cardiac arrest (heart suddenly stops beating): fatigue, loss of consciousness, dizziness, difficulty breathing, nausea, chest pain, or heart palpitations		✓	
Allergic reaction: difficulty swallowing, wheezing, drop in blood pressure, feeling sick to your stomach, vomiting, hives, rash, swelling of the face, lips, tongue or throat, itching, shortness of breath, difficulty breathing, skin redness, fast heart rate, sneezing, nausea, dizziness, or excessive sweating		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

NAROPIN will be stored by your healthcare professional or the hospital as follows:

- The medicine should be stored between 15 to 25°C in its carton prior to use.
- It should not be frozen.

Your healthcare professional should not use this medicine if they see particles in the ampoule or infusion bag, if the solution appears cloudy or discoloured, or if the product is leaking. Keep out of reach and sight of children.

If you want more information about NAROPIN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.aspenpharma.ca); or by calling 1-822-330-1213.

This leaflet was prepared by

Aspen Pharmacare Canada Inc.
201 - 2030 Bristol Circle, Oakville, ON, L6H 0H2

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