

# Naropin 2 mg/ml, 7.5 mg/ml and 10 mg/ml

Ropivacaine hydrochloride  
Solution for injection

## Composition

Name of the medicinal product	1 ml contains: ropivacaine hydrochloride (mg)	10 ml ampoule contains: ropivacaine hydrochloride (mg)	20 ml ampoule contains: ropivacaine hydrochloride(mg)
Naropin solution for injection			
2 mg/ml	2.0	20	40
7.5 mg/ml	7.5	75	150
10 mg/ml	10.0	100	200

For excipients see List of excipients.

## Pharmaceutical form

Solution for injection for perineural and epidural administration (10 and 20 ml).

Naropin solution for injection is a sterile, isotonic, isobaric, aqueous solution. The pH of the solution is adjusted to 4.0-6.0 with sodium hydroxide or hydrochloric acid and the solution is free from preservatives. The solutions are intended for single use only.

## Therapeutic indications

### Surgical anaesthesia

- Epidural block for surgery, including Caesarean section
- Major nerve block
- Field block

### Acute pain management

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

## Posology and method of administration

Naropin should only be used by or under the supervision of clinicians experienced in regional anaesthesia.

### Adults and children above 12 years of age:

The following table is a guide to dosage for the more commonly used blocks. The clinician's experience and knowledge of the patient's physical status are of importance when deciding the dose.

In general, surgical anaesthesia (e.g. epidural administration) requires the use of the higher concentrations and doses. For analgesia the 2 mg/ml concentration of Naropin is generally recommended.

## Dosage recommendations for Naropin in adults

	Conc. mg/ml	Volume ml	Dose mg	Onset min	Duration hours
<b>Surgical Anaesthesia</b>					
<b>Lumbar Epidural Administration</b>					
Surgery	7.5	15-25	113-188	10-20	3-5
	10.0	15-20	150-200	10-20	4-6
<b>Lumbar Epidural Administration</b>					
Caesarean Section	7.5	15-20	113-150	10-20	3-5
<b>Thoracic Epidural Administration</b>					
To establish block for postoperative pain relief	7.5	5-15	38-113	10-20	n/a
<b>Major Nerve Block</b>					
(e.g. brachial plexus)	7.5	10-40	75-300 <sup>1)</sup>	10-25	6-10
<b>Field Block</b>					
(e.g. minor nerve blocks and infiltration)	7.5	1-30	7.5-225	1-15	2-6

## Contraindications

Naropin solutions are contraindicated in patients with hypersensitivity to local anaesthetics of the amide-type.

## Special warnings and precautions for use

Regional anaesthetic procedures should always be performed in a properly equipped and staffed area. Equipment and drugs necessary for monitoring and emergency resuscitation should be immediately available. Patients receiving major blocks should be in an optimal condition and have an i.v. line inserted before the blocking procedure. The clinician responsible should take the necessary precautions to avoid intravascular injection (see Posology and method of administration) and be appropriately trained and familiar with the diagnosis and treatment of side effects, systemic toxicity and other complications (see Overdose).

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 an increased risk of intravascular injection and/or rapid systemic absorption, which can lead to high plasma concentrations.

Certain local anaesthetic procedures such as injections in the head and neck regions may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used.

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 anaesthesia is frequently the optimal anaesthetic technique in these patients. Patients treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive.

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 and in patients with concomitant heart disease. In some instances, resuscitation has been difficult. Should cardiac arrest occur, prolonged resuscitative efforts may be required to improve the possibility of a successful outcome.

Ropivacaine is metabolised in the liver. It should therefore be used with caution in patients with severe liver disease and repeated doses may need to be reduced due to delayed elimination. Normally there is no need to modify the dose in patients with impaired renal function when used for single-dose or short-term treatment. Acidosis and reduced plasma protein concentration, frequently seen in patients with chronic renal failure, may increase the risk of systemic toxicity.

Epidural anaesthesia may lead to hypotension and bradycardia. The risk of such effects can be reduced, e.g. by pre-loading the circulation or by injecting a vasopressor. Hypotension should be treated promptly with, for example, ephedrine 5-10 mg intravenously, repeated as necessary.

Prolonged administration of ropivacaine should be avoided in patients treated with strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin (see Interactions).

## Interactions

Naropin should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-

## Acute Pain Management

### Lumbar Epidural Administration

Bolus	2.0	10-20	20-40	10-15	0.5-1.5
Intermittent injections (top-up) (e.g. labour pain management)	2.0	10-15	20-30	(minimum interval 30 min)	

### Lumbar Epidural Administration

Continuous infusion e.g. Labour pain	2.0	6-10 ml/h	12-20 mg/h	n/a	n/a
Postoperative pain management	2.0	6-14 ml/h	12-28 mg/h	n/a	n/a

### Thoracic Epidural Administration

Continuous infusion (e.g. postoperative pain management)	2.0	6-14 ml/h	12-28 mg/h	n/a	n/a
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### Field Block

(e.g. minor nerve blocks and infiltration)	2.0	1-100	2-200	1-5	2-6
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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. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements. n/a = not applicable

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 the local anaesthetic used (see Special warnings and precautions for use).

In order to avoid intravascular injection, 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. When an epidural dose is to be injected, a preceding test dose of 3-5 ml lidocaine (Xylocaine 1-2%) with adrenaline is recommended. An inadvertent intravascular injection may be recognized by a temporary increase in heart rate and an accidental intrathecal injection by signs of a spinal block. If toxic symptoms occur, the injection should be stopped immediately.

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

When prolonged epidural 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. Cumulative doses up to 800 mg ropivacaine for surgery and postoperative analgesia administered over 24 hours were well tolerated in adults, as were postoperative continuous epidural infusions at rates up to 28 mg/hour for 72 hours.

For the treatment of postoperative pain, the following technique can be recommended: Unless preoperatively instituted, an epidural block with Naropin 7.5 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 opioids has been observed.

In clinical studies an epidural infusion of Naropin 2 mg/ml alone or mixed with fentanyl 1-4 µg/ml has been given for postoperative pain management for up to 72 hours. Naropin 2 mg/ml (6-14 ml/hour) provided adequate pain relief for the majority of patients. The combination of Naropin and fentanyl provided improved pain relief but caused opioid side effects.

For Caesarean section, neither intrathecal administration nor the use of the ropivacaine concentration 10 mg/ml for epidural administration, have been documented.

Until further experience has been gained, Naropin cannot be recommended for use in children below the age of 12 years.

type local anaesthetics, e.g. certain antiarrhythmics, such as lidocaine and mexiletin since the systemic toxic effects are additive. Specific interactions studies with ropivacaine and anti-arrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution is advised. (see Special warnings and precautions for use).

In healthy volunteers ropivacaine clearance was reduced by up to 77% during co-administration of fluvoxamine, a potent competitive inhibitor of P4501A2.

CYP1A2 is involved in the formation of 3-hydroxy-ropivacaine, a major metabolite. Thus strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin, given concomitantly with Naropin can cause a metabolic interaction leading to an increased ropivacaine plasma concentration. Prolonged administration of ropivacaine should therefore be avoided in patients treated with strong inhibitors of CYP1A2 such as fluvoxamine and enoxacin (see Special warnings and precautions for use).

## Pregnancy and lactation

### Pregnancy

Apart from obstetrical use, there are no adequate data on the use of ropivacaine in pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

### Lactation

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 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.

## Effects on ability to drive and use machines

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

## Undesirable effects

### General

The adverse reaction profile of Naropin is similar to that of other long-acting local anaesthetics of the amide-type.

As for other local anaesthetics, side effects reported after use of Naropin include physiological effects of the nerve block itself, e.g. hypotension, bradycardia and urinary retention after epidural 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).

The table of adverse drug reactions includes not only reactions caused by the drug per se but also frequently associated physiological side effects.

The percentage of patients that can be expected to experience adverse reactions varies with the route of administration of Naropin. Systemic adverse reactions of Naropin usually occur because of inadvertent intravascular injection, excessive dosage or rapid absorption.

## Table of adverse drug reactions

(Pooled data from all types of blocks)

Very common (>1/10)	<i>Vascular Disorders:</i> Hypotension <i>Gastrointestinal Disorders:</i> Nausea
Common (>1/100)	<i>Nervous System Disorders:</i> Paraesthesia, Dizziness, Headache <i>Cardiac Disorders:</i> Bradycardia, Tachycardia <i>Vascular Disorders:</i> Hypertension <i>Gastrointestinal Disorders:</i> Vomiting <i>Renal and Urinary Disorders:</i> Urinary retention <i>General Disorders and Administration Site Conditions:</i> Temperature elevation, Rigor, Back pain
Uncommon (>1/1,000)	<i>Psychiatric Disorders:</i> Anxiety <i>Nervous System Disorders:</i> Symptoms of CNS toxicity (Convulsions, Grand mal convulsions, Seizures, Light headedness, Circumoral paraesthesia, Numbness of the tongue, Hyperacusis, Tinnitus, Visual disturbances, Dysarthria, Muscular twitching, Tremor)*, Hypoaesthesia <i>Vascular Disorders:</i> Syncope <i>Respiratory, Thoracic and Mediastinal Disorders:</i> Dyspnoea <i>General Disorders and Administration Site Conditions:</i> Hypothermia
Rare (>1/10,000)	<i>Cardiac Disorders:</i> Cardiac arrest, Cardiac arrhythmias <i>General Disorder and Administration Site Conditions:</i> Allergic reactions (anaphylactic reactions, angioneurotic oedema and urticaria)

\* These symptoms usually occur because of inadvertent intravascular injection, overdose or rapid absorption (see Overdose).

### Class-related adverse drug reactions

This section includes complications related to the anaesthetic technique regardless of the local anaesthetic used.

#### Neurological complications

Neuropathy and spinal cord dysfunctions (e.g. anterior spinal artery syndrome, arachnoiditis, cauda equina), have been associated with epidural anaesthesia.

#### Total spinal block

Total spinal block may occur if an epidural dose is inadvertently administered intrathecally.

### Overdose

#### Acute systemic toxicity

Systemic toxic reactions primarily involve the central nervous system (CNS) and the cardiovascular system (CVS). Such reactions are caused by high blood concentration of a local anaesthetic, which may appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularized areas (see Special warnings and precautions for use). CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively.

Accidental intravascular injections of local anaesthetics may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, systemic toxicity appears later (15 – 60 minutes after injection) due to the slower increase in local anaesthetic blood concentration.

*Central nervous system toxicity* is a graded response with symptoms and signs of escalating severity. The first symptoms are usually light-headedness, circumoral paraesthesia, numbness of the tongue, hyperacusis, tinnitus and visual disturbances. Dysarthria, muscular twitching or tremors are more serious and precede the onset of generalized convulsions

### Pharmacokinetic properties

Ropivacaine has a chiral centre and is the pure S-(-)-enantiomer. Ropivacaine has a  $pK_a$  of 8.1 and a distribution ratio of 141 (25°C n-octanol/ phosphate buffer pH 7.4). The metabolites have a pharmacological activity that is less than that of ropivacaine.

The plasma concentration of ropivacaine depends on the dose, the route of administration 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, with half-lives of the two phases of 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 has a mean total plasma clearance of the order of 440 ml/min, an unbound plasma clearance of 8 l/min, a renal clearance of 1 ml/min, a volume of distribution at steady state of 47 l and a terminal half-life of 1.8 h after i.v. administration. Ropivacaine has an intermediate hepatic extraction ratio of about 0.4. It is mainly bound to  $\alpha_1$ -acid glycoprotein in plasma with an unbound fraction of about 6%.

An increase in total plasma concentrations during continuous epidural and interscalene infusion has been observed, related to a postoperative increase of  $\alpha_1$ -acid glycoprotein. Variations in unbound, i.e. pharmacologically active, 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 foetus is less than in the mother, which results in lower total plasma concentrations in the foetus.

Ropivacaine is extensively metabolised in the liver, predominantly by aromatic hydroxylation to 3-hydroxy-ropivacaine mediated by cytochrome P4501A2, and N-dealkylation to PPX mediated by CYP3A4. After single i.v. administration approximately 37% of the total dose is excreted in the urine as both free and conjugated 3-hydroxy-ropivacaine, the major metabolite. Low concentrations of 3-hydroxy-ropivacaine have been found in the plasma. Urinary excretion of the PPX and other metabolites account for less than 3% of the dose.

During epidural infusion, both PPX and 3-hydroxy-ropivacaine are the major metabolites excreted in the urine. Total PPX concentration in the plasma was about half of that of total ropivacaine, however, mean unbound concentrations of PPX was about 7 to 9 times higher than that of unbound ropivacaine following continuous epidural infusion up to 72 hours. The threshold for CNS-toxic unbound plasma concentrations of PPX in rats is about twelve times higher than that of unbound ropivacaine.

There is no evidence of *in vivo* racemization of ropivacaine.

### List of excipients

Sodium chloride, Hydrochloric acid, Sodium hydroxide, Water for injections.

### Incompatibilities

Alkalisiation may lead to precipitation since ropivacaine is poorly soluble above pH 6.0.

### Shelf-life

Please refer to expiry date on the outer carton.

### Special precautions for storage

Do not store above 30°C. Do not freeze.

### Pack size

Please refer to outer carton for pack size.

### Instructions for use and handling

more serious and precede the onset of generalized convulsions. These signs must not be mistaken for neurotic behaviour. Unconsciousness and grand mal convulsions may follow, which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly during convulsions due to the increased muscular activity, together with the interference with respiration. In severe cases apnoea may occur. The acidosis increases and extends the toxic effects of local anaesthetics.

Recovery follows the redistribution of the local anaesthetic drug from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the drug have been injected.

*Cardiovascular 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 benzodiazepines or barbiturates. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics.

#### **Treatment of acute systemic toxicity**

If signs of acute systemic toxicity occur, injection of the local anaesthetic should be stopped immediately.

In the event of convulsions, treatment will be required. The objectives of treatment are to maintain oxygenation, stop the convulsions and support the circulation. Oxygen must be given and ventilation assisted, when necessary (mask and bag or tracheal intubation). An anticonvulsant should be given i.v. if the convulsions do not stop spontaneously in 15-20 seconds. Thiopentone sodium 1-3 mg/kg i.v. will abort the convulsions rapidly. Alternatively diazepam 0.1 mg/kg i.v. may be used, although its action will be slow. Prolonged convulsions may jeopardize the patient's ventilation and oxygenation. If so, injection of a muscle relaxant (e.g. succinylcholine 1 mg/kg) will rapidly stop the convulsions so that ventilation and oxygenation can be controlled. Endotracheal intubation must be considered in such situations.

If cardiovascular depression is evident (hypotension, bradycardia), ephedrine 5-10 mg i.v. should be given and this dose should be repeated, if necessary, after 2-3 minutes.

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 possibility of a successful outcome.

Instructions for use and handling  
The products are free from preservatives and are intended for single use only. Any solution remaining from an opened container should be discarded.

The intact container must not be re-autoclaved. A blister container should be chosen when a sterile exterior is required.

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AstraZeneca AB, Södertälje, Sweden.

## Pharmacodynamic properties

Pharmacotherapeutic group (ATC code): N01B B09

Ropivacaine is a long-acting, amide-type local anaesthetic with both anaesthetic and analgesic effects. At high doses it produces surgical anaesthesia, while at lower doses it produces sensory block (analgesia) with limited and non-progressive motor block.

Onset and duration of the local anaesthetic effect of Naropin depend on the dose and site of administration, while presence of a vasoconstrictor (e.g. adrenaline) has little, if any influence.

Ropivacaine, 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.

Local anaesthetics may have similar effects on other excitable membranes e.g. in the brain and myocardium. If excessive amounts of drug reach the systemic circulation, symptoms and signs of toxicity may appear, emanating from the central nervous and cardiovascular systems.

Cardiac effects measured *in vivo* in animal studies showed that ropivacaine has a lower cardiac toxicity than bupivacaine.

Pregnant ewes showed no greater sensitivity to systemic toxic effects of ropivacaine than non-pregnant ewes.

Healthy volunteers exposed to intravenous infusions of CNS toxic doses showed significantly less cardiac effects after ropivacaine than after bupivacaine.

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