NAROPIN 7.5 mg/ml

ropivacaine hydrochloride

Solution for injection

Qualitative and quantitative composition

Name of the medicinal product	1 ml contains ropivacaine hydrochloride (mg)	20 ml ampoule contains Ropivacaine hydrochloride (mg)
NAROPIN 7.5 mg/ml	7.5	150

For excipients see *List of excipients*.

Pharmaceutical form

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

NAROPIN is indicated for:

Surgical anaesthesia

- Epidural block for surgery, including Caesarean section
- Peripheral nerve blocks and infiltration anaesthesia

Acute pain management

- Continuous epidural infusion or intermittent bolus administration e.g. post operative or labour pain
- Peripheral nerve blocks and infiltration anaesthesia

Posology and method of administration

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

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 (e.g. epidural administration for acute pain management) the lower concentrations and doses are recommended.

Dosage Recommendations for NAROPIN

	Conc. mg/ml	Volume ml	Dose mg	Onset minutes	Duration hours
SURGICAL ANAESTHESIA					
Lumbar Epidural Administration					
Surgery	7.5	15-25	113-188	10-20	3-5
Lumbar Epidural Administration					
Caesarean section	7.5	15-20	113-150	10-20	3-5
Thoracic Epidural Administration					
To establish block for post-operative pain relief	7.5	5-15	38-113	10-20	n/a
Field Block					
(e.g. minor nerve blocks and infiltration)	7.5	1-30	7.5-225	1-15	2-6
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 (minimum interval 30 minutes)	20-30		
Lumbar Epidural Administration					
Continuous infusion (e.g. labour pain and postoperative pain management)	2.0	6-14 ml/h	12-28 mg/h	n/a	n/a
Thoracic Epidural Administration					
To establish block for post-operative pain relief	2.0	4-8 ml/h	8-16 mg/h	n/a	n/a
Field Block					
(e.g. minor nerve blocks and infiltration)	2.0	1-100	2-200	1-5	2-6

In caesarean section, incremental dosing should be applied the starting dose of about 100 mg to be given over 3-5 minutes. Two additional doses each of 25 mg may be administered as needed. The total administration doses should not exceed 150 mg.

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.

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 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. Experience to date indicates that a cumulative dose of about 800 mg ropivacaine administered over 24 hours is well tolerated in adults.

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 6-10 ml (12-20 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. Clinical studies also show, however, that some patients require higher doses. Infusion rates of 12-14 ml (24-28 mg) per hour have been well tolerated.

Concentrations above 7.5 mg/ml have not been documented for Caesarean section.

Clinical experience supports the use of NAROPIN epidural infusions for up to 24 hours. Until further experience has been gained, NAROPIN cannot be recommended for use in children below the age of 12 years.

Contraindications

NAROPIN solutions are contraindicated in patients with known hypersensitivity to local anaesthetics of the amide type. General contra-indications related to epidural anaesthesia, regardless of the local anaesthetic used, should be taken into account. Intravenous regional anaesthesia. Obstetric paracervical anaesthesia. Hypovolaemia

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 or in high doses should in an optimal condition and have an IV line inserted before the blocking procedure. The clinician responsible should take the necessary precautions to avoid intravascular injection (see section *Posology and method of administration*) and be appropriately trained and familiar with diagnosis and treatment of side effects, systemic toxicity and other complications such as inadvertent subarachnoid injection, which may produce a high spinal block with apnoea and hypotension.

Convulsions have occurred most often after brachial plexus block and epidural block. This is likely to be the result of either accidental intravascular injection or rapid absorption from the injection site (see section *Overdose*).

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. Caution is required to prevent injections in inflamed areas.

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 indicated in these patients. To

reduce the risk of potentially serious adverse reactions, attempts should be made to optimize the patient's condition before major blocks are performed and the dosage should be adjusted accordingly.

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 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 metabolized 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 and intrathecal anaesthesia may lead to hypotension and bradycardia. The risk of such effects can be reduced, e.g. by injecting a vasopressor. Hypotension should be treated promptly with sympathomimetic intravenously and repeated as necessary. In the event of overdose or inadvertent intravascular injection toxic symptom from CNS (convulsion, altered conscious states) and/or the cardiovascular system (arrhythmias, hypotension, myocardial depression) may appear.

Patients with hypovolaemia due to any cause can develop sudden and severe hypotension during epidural anaesthesia, regardless of the local anaesthetic used.

A possible cross-hypersensitivity with other amide-type local anaesthetics should be taken into account.

Prolonged administration of ropivacaine should be avoided in patients concomitantly treated with strong CYP1A2 inhibitors, such as fluvoxamine and enoxacin (see section *Interaction with other medicaments and other forms of interaction).*

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

There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics. The majority of reported cases of chondrolysis have involved the shoulder joint. Due to multiple contributing factors and inconsistency in the scientific literature regarding mechanism of action, causality has not been established. Intra-articular continuous infusion is not an approved indication for NAROPIN.

Interaction with other medicaments and other forms of interaction

NAROPIN should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics such as lidocaine and mexitetine, since the 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 section *Special warnings and precautions for use*). Simultaneous use of NAROPIN with general anaesthetics or opioids may potentiate each others (adverse) effects. There is a potential risk for metabolic interaction when NAROPIN is used in combination with CYPIA-Inhibitors, e.g. fluvoxamine and verapamil, which may result in increased plasma levels of NAROPIN.

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 section *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 human pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/ foetal development, parturition or postnatal development. Intrathecal administration has not been documented for Caesarean section.

Lactation

The excretion of ropivacaine and 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

The adverse event profile of NAROPIN is similar to those of other amide local anaesthetics. Adverse reactions caused by the drug *per se* are difficult to distinguish from the physiological

effects of the nerve block (e.g. decrease in blood pressure, bradycardia), events caused directly (e.g. nerve trauma) or indirectly (e.g. epidural abscess) by the needle puncture.

Very common (>10%)

Vascular disorders	: Hypotension[c]
Gastrointestinal disorders	: Nausea

Common (>1%)

Nervous system disorders	: Paraesthesia, dizziness, headache[a]
Cardiac disorders	: Bradycardia[a], tachycardia
Vascular disorders	: Hypertension
Gastrointestinal disorders	: Vomiting[a,d]
Renal and urinary disorders	: Urinary retention[a]
General disorders and administration site conditions	: Temperature elevation, rigor, back pain, insomnia, chest pain, pain and oliguria.

Uncommon (≤ 1%)

Psychiatric disorders	: Anxiety
Nervous system disorders	: 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) [b], Hypoaesthesia[a]
Vascular disorders	: Syncope[a]
Respiratory, thoracic and mediastinal disorders	: Dyspnoea[a]
General disorders and administration site conditions	: Hypothermia[a]

Rare (≤ 0.1%)

Cardiac disorders	: Cardiac arrest, cardiac arrhythmias
General disorder and administration site condition	: Allergic reactions (anaphylactic reactions, angioneurotic oedema and urticaria)

[a] These reactions are more frequent after spinal anaesthesia.

[b] These symptoms usually occur because of inadvertent intravascular injection, overdose or rapid absorption.

[c] Hypotension is less frequent in children (> 1%)

[d] Vomiting is more frequent in children (> 10%)

Class related adverse drug reactions

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

Neurological complications

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

Total spinal block

Total spinal block may occur if an epidural dose is inadvertently administered intrathecally or if a too large intrathecal dose is administered.

Foetal, neonatal and infant adverse events

Clinical trials have been conducted in over 400 pregnant women using NAROPIN. These studies recorded all adverse events experienced by the baby in utero, peri- or postpartum, regardless of causality to NAROPIN, other medications or other factors.

Common (>1%)

Cardiovascular disorders	: Foetal distress, foetal tachycardia and foetal bradycardia.
Gastrointestinal disorders	: Neonatal vomiting.
Respiratory disorders	: Neonatal respiratory disorders and neonatal tachypnoea.
Other	: Neonatal fever and neonatal jaundice.

Uncommon events (<1%)

Metabolic disorders	: Foetal acidosis and neonatal hypoglycaemia.
Other	: Hypotonia, neonatal sepsis and low Apgar score.

Overdose

Acute systemic toxicity

Systemic toxic reactions primarily may involve the central nervous system and the cardiovascular system. 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 vascularised areas. CNS reactions are similar for

all amide local anaesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively.

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 generalised 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 and possible loss of functional airways. In severe cases even apnoea may occur. Acidosis hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

Recovery is due to 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 may be seen in severe cases and is generally preceded by signs of toxicity in the central nervous system. In patients under heavy sedation or receiving a general anaesthetic, prodromal CNS symptoms may be absent. Hypotension, bradycardia, arrhythmia, and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics, but in rare cases cardiac arrest has occurred without prodromal CNS effects.

In children, early signs of local anaesthetic toxicity may be difficult to detect since they may not be able to verbally express them, or if they are under general anaesthesia.

Treatment of acute toxicity

If signs of acute systemic toxicity appear, injection of the local anaesthetic should be stopped immediately and CNS symptoms (convulsion, CNS depression) must promptly be treated with appropriate airway/respiratory support and the administration of anticonvulsant drugs.

If circulatory arrest should occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

If cardiovascular depression is evident (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, and or inotropic agents should be considered. Children should be given ephedrine doses commensurate with their age and weight.

Should cardiac arrest occur, a successful outcome may require prolonged resuscitative efforts.

Oxygen must be given and ventilation assisted, when necessary (mask and bag or tracheal intubation). An anticonvulsant should be given IV if the convulsions do not stop spontaneously in 15-20 seconds, thiopentone 100-150 mg IV will abort the convulsions rapidly. Alternatively diazepam 5-10 mg IV may be used, although its action is slower. 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. Suxamethonium will stop the muscle convulsions rapidly, but the patient will require tracheal intubation and controlled ventilation.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group (ATC code): N01B B09.

Ropivacaine is the 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.

Central nervous system toxicity (see section *Overdose*) precedes the cardiovascular effects since it occurs at lower plasma concentrations. Minor cardiovascular effects have been observed after therapeutically active doses of ropivacaine in animal studies in vivo. Direct effect of local anaesthetics on the heart include slowing of conduction, negative inotropism and, eventually, arrhythmias and cardiac arrest. High intravenous doses of ropivacaine induce similar effects.

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

Pharmacokinetics

Ropivacaine has a chiral centre and is the pure S-(-)-enantiomer. Ropivacaine has a pKa of 8.1 and a distribution ratio of 141 (25C 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 upon 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 litres and a terminal half-life of 1.8 h after IV administration. Ropivacaine has an

intermediate hepatic extraction ratio of about 0.4. It is mainly bound to α_1-1acid 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 postoperative increase of α1-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 fetus is less than in the mother, which results in lower total plasma concentrations in the fetus.

Ropivacaine is extensively metabolized in the liver, predominantly by aromatic hydroxylation to 3-hydroxyropivacaine mediated by cytochrome P4501A2 and N-dealkylation to PPX mediated by CYP3A4. After single IV administration approximately 37% of the total dose is excreted in the urine as both free and conjugated 3-hydroxyropivacaine, the major metabolite. Urinary excretion of the PPX and other metabolites account for less than 3% of the dose.

Impaired renal function has little or no influence on ropivacaine pharmacokinetics. The renal clearance of 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 PPX includes a non-renal elimination in addition to renal excretion. Some patients with impaired renal function may show an increased exposure to PPX resulting from a low non-renal clearance. Due to the reduced CNS toxicity of PPX as compared to ropivacaine the clinical consequences are considered negligible in short-term treatment.

In total 86% of the dose is excreted in the urine after intravenous administration of which only about 1% relates to unchanged drug. Conjugated + unconjugated 3-hydroxyropivacaine shows only detectable concentrations in plasma. 3-hydroxy- and –4-hydroxy-ropivacaine have a local anaesthetic activity although less than that of ropivacaine.

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

List of excipients

Sodium chloride, hydrochloric acid, sodium hydroxide, water for injections.

Incompatibilities

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

Shelf life

Please refer to expiry date on the blister strip or outer carton.

Special precaution for storage

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

Pack size

Box, 5 Polyamp Duofit @ 20 ml in sterile blister packs

Reg. No.: DKI1951303843A1

The polypropylene ampoules (Polyamp) are specially designed to fit Luer lock and Luer fit syringes.

Instruction for use/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 outside is required.

HARUS DENGAN RESEP DOKTER

Manufactured by:

AstraZeneca AB, Södertälje, Sweden for Aspen Global Incorporated

Imported by:

PT Mitsubishi Tanabe Pharma Indonesia

Bandung, Indonesia

Date of revision of text

11 Aug 2015

Doc ID-002986106