PS15765

Naropin

(Ropivacaine Hydrochloride)

PRODUCT INFORMATION

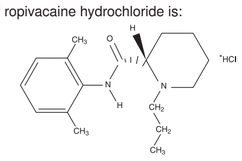
(Injection solutions for the production of local or regional anaesthesia)

NOT FOR INTRAVENOUS ADMINISTRATION UNDER ANY CIRCUMSTANCES

NAME OF THE MEDICINE

The active ingredient in NAROPIN is ropivacaine hydrochloride. The CAS number for the free base is 84057-95-4. The chemical formula of ropivacaine hydrochloride is $C_{17}H_{26}N_2O.HCl.H_2O$.

The chemical structure of ropivacaine hydrochloride is:



DESCRIPTION

The chemical name for ropivacaine hydrochloride is (S)-(-)-propyl-piperidine-2-carboxylic acid (2,6-dimethyl-phenyl)-amide hydrochloride monohydrate. It is a white crystalline powder and has a water solubility of about 50 mg/mL. Ropivacaine hydrochloride was developed as the pure S-(-)-isomer and has an enantiomeric purity of > 99%. It has a pKa of 8.1 (at 25 °C) and a molecular weight of 328.89. The pH of a saturated solution of ropivacaine hydrochloride is 4.5 and that of a 1% (w/v) aqueous solution is 5.0.

NAROPIN solution for injection is a sterile, isotonic, isobaric, aqueous solution of ropivacaine HCl in Water for Injections BP. The pH of the solution is adjusted with sodium hydroxide or hydrochloric acid to remain between 4.0 - 6.0 during the approved shelf-life. The nominal osmolality of NAROPIN 0.2% (2 mg/mL) is 288 mosmol/kg. The solution is preservative free.

The presentations of NAROPIN injection solutions are intended for single use only. Any solution remaining from an opened container should be discarded.

PHARMACOLOGY

Ropivacaine has both anaesthetic and analgesic effects. At higher doses it produces surgical anaesthesia with motor block, while at lower doses it produces a sensory block including analgesia with little motor block.

The duration and intensity of ropivacaine sensory block is not improved by the addition of adrenaline.

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. It is the first long acting amide local anaesthetic developed as a pure enantiomer. There is no evidence of *in vivo* racemisation of ropivacaine.

Pharmacodynamics and tolerability

The local anaesthetic effect of ropivacaine and its R-(+) enantiomer was evaluated for sciatic block, spinal anaesthesia and infiltration anaesthesia over a wide concentration range (0.25 - 1.0%) in a number of animal species and a concentration-(dose-) response relationship was ascertained. These studies supported the selection of the enantiomerically pure drug ropivacaine and are consistent with the observations with other local anaesthetics that the S-(-) form is less toxic and/or has a longer duration of action than the R-(+) form.

In vitro testing of ropivacaine conduction anaesthesia indicate that ropivacaine is comparable to, or slightly more potent than, bupivacaine in blocking sensory fibres and is less active in blocking motor fibres.

The anaesthetic effects of ropivacaine were evaluated in peripheral (sciatic nerve and brachial plexus) and central (spinal and epidural) neural blocks, as well as in infiltration and topical anaesthesia in a large number of studies using multiple animal species including mouse, rat, guinea-pig, dog, sheep and Rhesus monkey.

The peripheral neural block studies indicate that a concentration of ropivacaine of 0.5 - 1.0% consistently produces effective sensory and motor block. Neither increasing concentration above 0.75% nor adding adrenaline significantly improved the duration of motor block or anaesthesia with ropivacaine.

For central neural blockade, for all species studied, it appeared that onset times of epidural anaesthesia with ropivacaine and bupivacaine were similar. The concentration required to consistently produce complete motor blockade with epidural anaesthesia appeared to be 0.75 - 1.0% for ropivacaine. Duration of sensory block appeared to be comparable for equal concentrations of ropivacaine and bupivacaine.

Tests of infiltration anaesthesia in guinea-pigs showed that ropivacaine was markedly superior to bupivacaine in producing sustained cutaneous anaesthesia at all concentrations. The duration of anaesthesia produced with the least effective ropivacaine concentration (0.25%) far exceeded that produced by the highest bupivacaine concentration (0.75%).

For analgesia, the potency of ropivacaine is similar to that of bupivacaine. For motor block, the potency was found to be around 80% of bupivacaine.

Ropivacaine and bupivacaine are equipotent in producing seizures in rats and dogs. In both pregnant and non-pregnant sheep, ropivacaine was less toxic than bupivacaine.

Comparisons with the short acting local anaesthetic lignocaine shows that the doses needed to produce seizures are 2 (in sheep) to 4 (in rats and dogs) times the dose of ropivacaine. In studies in sheep, ropivacaine appears to have less central nervous system and cardiovascular toxicity than bupivacaine, and pregnancy does not appear to enhance sensitivity in either the central nervous system or in cardiac membranes as has been reported in some studies with bupivacaine.

In vitro heart studies indicate that the effects of ropivacaine on conduction and contractility are less compared to bupivacaine. The risk of ventricular tachycardia is less with ropivacaine than bupivacaine. Atrial and ventricular pacing were more successful during exposure to high concentrations of ropivacaine compared to bupivacaine. The *in vitro* electrophysiological studies are consistent with the findings in the *in vitro* heart preparation.

Cardiovascular effects measured *in vivo* in animal studies showed that ropivacaine is consistently well tolerated and that ropivacaine is less likely than bupivacaine to produce ventricular arrhythmias. Resuscitative measures were highly successful in dogs given large overdoses (9.8 mg/kg given intravenously) of ropivacaine. In most preclinical studies of the cardiovascular effects, comparisons were also made with lignocaine. In general all results were consistent with the observation that a given dose of lignocaine was less toxic than an equivalent dose of ropivacaine or bupivacaine.

In man, ropivacaine is less toxic regarding the CNS and cardiovascular systems than bupivacaine. In two tolerability studies in volunteers given IV infusions, CNS symptoms appeared at higher doses and higher free plasma concentrations of ropivacaine compared to bupivacaine. The ropivacaine dose-response and concentration-response curves for CNS symptoms, e.g. muscular twitching, dysarthria, were consistently shifted to the right compared with those of bupivacaine. A threshold for CNS toxicity was apparent at a free plasma concentration of 0.34mg/L ropivacaine and 0.13mg/L bupivacaine. Ropivacaine caused a smaller increase in the QRS width and less pronounced reduction in diastolic and systolic function of the left ventricle as compared to bupivacaine.

2,6-pipecoloxylidide (PPX) is an inactive metabolite. The threshold for systemic CNS-toxic unbound plasma concentrations of PPX in rats is about twelve times higher than that of unbound ropivacaine.

Factors which may increase the relative systemic toxicity of local anaesthetics are acidosis and severe hepatic dysfunction.

Ropivacaine, like bupivacaine and other local anaesthetics, produces vasoconstriction at lower concentrations and vasodilation at higher concentrations. These findings appear to be consistent both *in vivo* and *in vitro*.

Pharmacodynamic interactions

In preclinical studies in rats, ropivacaine interacts with agents used in conjunction with regional anaesthesia, such as benzodiazepines, thiopental, enflurane, pancuronium, suxamethonium and fentanyl, in a manner similar to that produced by the commonly used local anaesthetics bupivacaine and lignocaine. In rats, pretreatment with ropivacaine potentiated the sedative effect of morphine compared to placebo.

Pharmacodynamic drug interactions of local anaesthetics probably depend more on the physiological effects of the block, such as hypotension and bradycardia, than on circulating blood levels of the local anaesthetic.

Pharmacokinetics

The plasma concentration of ropivacaine depends upon the dose, the route of administration and the vascularity of the injection site. Ropivacaine has 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 in the order of 14 minutes and 4 hours. 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 a biphasic absorption from the caudal epidural space also in children.

The pharmacokinetic profile of ropivacaine in adults following experimental IV administration is summarised below:

Plasma clearance	440 mL/min
Unbound plasma clearance	8 L/min
Renal clearance	1 mL/min
Volume of distribution at steady-state	47 L
Unbound volume of distribution at steady-state	819 L
Terminal half-life	1.8 h
Unbound fraction	0.06
Hepatic extraction ratio	0.4
Major metabolite	3-OH-ropivacaine

Ropivacaine is mainly bound to α_1-acid glycoprotein in plasma with an unbound pharmacologically active fraction of about 6%. An increase in total plasma concentrations during continuous postoperative epidural infusion and interscalene infusion has been observed. This increase is related to a postoperative increase of α_1-acid glycoprotein. Variations in unbound concentration of ropivacaine have been much less than in total plasma concentration.

Ropivacaine is extensively metabolised, predominantly by aromatic hydroxylation. In total, 86% of the dose is excreted in the urine after intravenous administration, of which only about 1% is unchanged drug. Approximately 9% is excreted in faeces.

Both the dealkylation (N-depropylated or PPX) and the hydroxylation pathways in the metabolism of ropivacaine are detoxification reactions. PPX is considered to have approximately one twelfth of the pharmacological activity of ropivacaine. The hydroxylated metabolites of ropivacaine have some local anaesthetic activity (ropivacaine > 3-hydroxy-ropivacaine >> 4-hydroxy-ropivacaine). The hydroxylated metabolites are rapidly conjugated in human plasma and are very unlikely to have any pharmacological or toxicological activities.

The major metabolite is 3-hydroxy-ropivacaine. This metabolite accounts for about 37% of urinary excretion, mainly as a glucuronide conjugate. The only metabolite which reaches detectable concentrations in plasma is 3-hydroxy-ropivacaine (conjugated and unconjugated). Urinary excretion of 4-hydroxy-ropivacaine, the N-dealkylated metabolite and the 4-hydroxy-dealkylated metabolite accounts for 1 - 3% of a given dose.

The NADPH-dependent metabolism of ropivacaine to 3-hydroxy-ropivacaine is catalysed by CYP1A2. The formation of minor metabolites *in vivo* is catalysed by CYP3A4. The apparent Km (affinity constant) for 3-hydroxy-ropivacaine is 16 µM and about 400 µM for the other metabolites. Of the two members in the CYP1A family, CYP1A1 is expressed only after exposure to inducers, while CYP1A2 accounts for about 10% of total P450 in the liver (see METABOLIC INTERACTIONS).

A similar pattern of metabolites has been found in children above one year.

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. The potential for toxicity in these patients is dependent on the total dose, dose route and duration of exposure to ropivacaine.

Paediatrics

The pharmacokinetics of ropivacaine was characterized in a pooled population PK analysis on data in 192 children between 0 and 12 years from six studies (3 on caudals, 2 on epidural infusions, and 1 on ilioinguinal block). Unbound ropivacaine and PPX clearance and ropivacaine unbound volume of distribution initially depend on both body weight and age up to three years of age, after which they depend largely on body weight. The maturation of unbound ropivacaine clearance appears to be complete by the age of 3 years, that of PPX by the age of 1 year and unbound ropivacaine volume of distribution by the age of 2 years. The PPX unbound volume of distribution only depends on body weight.

Unbound ropivacaine clearance increases from 2.4 and 3.6 L/h/kg in the newborn and the 1-month neonate to about 8-16 L/h/kg for ages above 6 months, values within the range of those in adults. Total ropivacaine clearance values per kg body weight increase from about 0.10 and 0.15 L/h/kg in the newborn and the 1-month neonate to about 0.3 - 0.6 L/h/kg beyond the age of 6 months. Unbound ropivacaine volume of distribution per kg body weight increases from 22 and 26 L/kg in the newborn and the 1-month neonate to 42 - 66 L/kg above 6 months. Total ropivacaine volume of distribution per kg body weight increases from 0.9 and 1.0 L/kg for the newborn and the 1-month neonate to 1.7 - 2.6 L/kg beyond the age of 6 months. The terminal half-life of ropivacaine is longer, 6 to 5 h in the newborn and the 1-month neonate compared to about 3 h in older children. The terminal half-life of PPX is also longer, from 43 and 26 h in the newborn and the 1-month old neonate to about 15 h in older children.

At 6 months, the breakpoint for change in the recommended dose rate for continuous epidural infusion, unbound ropivacaine clearance has reached 34% and unbound PPX 71% of its mature value. The systemic exposure is higher in neonates and also somewhat higher in infants between 1 to 6 months compared to older children which is related to the immaturity of their liver function. However, this is partly compensated for by the recommended 50% lower dose rate for continuous infusion in infants below 6 months.

Simulations on the sum of unbound plasma concentrations of ropivacaine and PPX, based on the PK parameters and their variance in the population analysis, indicate that for a single caudal block the recommended dose must be increased by a factor of 2.7 in the youngest group and a factor of 7.4 in the 1 to 10 year group in order for the upper prediction 90% confidence interval limit to touch the threshold for adult systemic toxicity. Corresponding factors for the continuous epidural infusion are 1.8 and 3.8 respectively.

When comparing descriptive data in a trial of caudal/epidural infusions in 10 full term neonates aged 0-30 days, to that in 18 older patients aged 31-180 days, total and unbound ropivacaine was higher and showed higher inter-individual variability, unbound apparent clearance lower and ropivacaine binding to plasma proteins (AAG) was lower. There was a greater relative excretion of ropivacaine in urine. Plasma concentrations of total and unbound PPX were similar but PPX had a longer half-life. The sum of unbound concentrations of ropivacaine and one twelfth of PPX was higher in neonates 0-7 days. While the highest level reached was 0.24 mg/L, this may have been still rising when observations ceased at 72 h (only 4 observations). The systemic CNS toxicity threshold in adults is 0.34 mg/L in a mature nervous system (see Pharmacodynamics and tolerability). It is not known how immaturity of the CNS affects toxic thresholds.

Foetuses exposed to ropivacaine during labour or Caesarean section can be regarded, after they have been born, as neonates with a peak plasma concentration at the time of delivery. The maximum unbound plasma ropivacaine concentrations in the newborn as reflected in the umbilical vein at delivery, 0.03 to 0.11 mg/L, are in the same range as those seen after single caudal block in neonates and support the documentation of ropivacaine in neonates.

Neonatal exposure based on umbilical venous plasma concentrations at delivery after epidural block for Caesarean section with ropivacaine 115 to 150 mg or continuous lumbar epidural infusion with 25 mg/h in labour.

Delivery		n	Mean	SD	Median	Min	Max
Caesarean section	C_{max} (mg/L)	71	0.33	0.16	0.30	0.11	1.12
	$C_{u,\,max}$ (mg/L)	69	0.07	0.02	0.07	0.03	0.11
	f_u (%)	69	21.6	6.6	22.2	6.1	34.4
Labour	C_{max} (mg/L)	10	0.32	0.13	0.34	0.13	0.52
	$C_{u,\,max}$ (mg/L)	10	0.05	0.01	0.04	0.03	0.07
	f_u (%)	10	16.8	8.6	12.5	8.5	30.2

Pharmacokinetics during pregnancy at term

In pregnancy at term, ropivacaine clearance is somewhat lower and its unbound clearance about half of that seen after epidural administration to non-pregnant patients. Accordingly, total C_{max} and unbound C_{max} are higher in pregnancy. The unbound plasma concentrations in the umbilical vein at delivery were similar to those in the mother and showed a fairly rapid equilibrium. There was no obvious correlation between neonatal neurologic and adaptive capacity scores and unbound or total plasma concentrations in the newborns.

Epidural Injection

Two parallel groups of 10 patients each, scheduled for epidural analgesia to relieve pain during labour, received ropivacaine or bupivacaine as a 50 mg bolus followed on request by a 25 mg top-up dose.

The unbound concentration of ropivacaine was higher than that of bupivacaine at 20 min, 0.04 (0.013) mg/L and 0.02 (0.008) mg/L as well as at 4 hours after the initial dose, 0.03 (0.006) mg/L and 0.02 (0.013) mg/L. The mean unbound fraction of ropivacaine was higher, 0.07, than that of bupivacaine, 0.04.

Epidural Infusion

Patients scheduled for epidural analgesia as pain relief during labour received a continuous lumbar epidural infusion of ropivacaine 12.5 mg/h, 25 mg/h or bupivacaine 25 mg/h after an initial dose of 12.5 mg (ropivacaine) or 25 mg (ropivacaine or bupivacaine). Treatment with ropivacaine 12.5 mg/h was terminated after 6 patients had been withdrawn due to insufficient analgesia. The results in the two groups of 10 patients each given 25 mg/h of ropivacaine or bupivacaine (2.5 mg/mL) are described below. The rate of infusion (dose) was not changed during the course of the study.

The median duration of the infusion was 6.6 hours with ropivacaine and 7.7 hours with bupivacaine, corresponding to total mean doses of 179 and 227 mg.

The maternal unbound fraction was higher after ropivacaine than after bupivacaine. The unbound plasma clearance of ropivacaine, 3.35 (1.36) L/min, was about half of that of bupivacaine, 6.40 (2.47 L/min). The mean (SD) umbilical venous unbound fraction was 0.17 (0.09) with ropivacaine and 0.12 (0.05) with bupivacaine. The unbound UV/MV ratios did not seem to increase with the duration of the infusion, indicating rapid equilibration.

Umbilical arterial (UA) and venous (UV) unbound concentrations after continuous lumbar epidural infusion of ropivacaine and bupivacaine 25 mg/h in labour are presented in the following table.

Umbilical arterial (UA) and venous (UV) unbound concentrations after continuous lumbar epidural infusion of ropivacaine and bupivacaine 25 mg/h in labour.

		UA Free (mg/L)
Ropivacaine Actual total dose given of ropivacaine HCl 145 - 200 mg		0.027 – 0.058 (n=4)
	Median	**0.036**
Bupivacaine Actual total dose given of bupivacaine HCl 93.5 - 227.4 mg		0.014 – 0.21 (n=2)
	Median	**0.017**
		UV Free (mg/L)
Ropivacaine Actual total dose given of ropivacaine HCl 99.2 - 255.4 mg		0.027 – 0.067 (n=10)
	Median	**0.042**
Bupivacaine Actual total dose given of bupivacaine HCl 93.5 - 365.3 mg		0.011 – 0.035 (n=9)
	Median	**0.025**

CLINICAL TRIALS

Adults

Two open label, randomized uncontrolled clinical studies were performed to document the efficacy and safety of NAROPIN 2 mg/mL in continuous peripheral nerve block for post-operative management up to 48 hours. In total 163 patients were studied, 136 received femoral block and 27 interscalene block. Continuous peripheral nerve blocks with ropivacaine provided effective post operative pain relief in both studies. Patient satisfaction was reported to be high.

Paediatrics

A total of 5 studies, involving 246 patients aged 0-12 years, were performed to evaluate the use of NAROPIN 2 mg/mL (0.2%) for caudal block (3 studies) and continuous epidural infusion (2 studies). In the studies on caudal block, the given volumes of the ropivacaine solutions were 1 mL/kg. In one of these studies in paediatric patients between 4 and 12 years of age, three different dosages of NAROPIN (1, 2 and 3 mg/kg, 0.1%, 0.2% and 0.3%) were compared. Adequate efficacy with minimal motorblock was found for the 2 mg/kg dose. In another study on caudal block in neonates and infants between 0 and 12 months of age, the analgesic efficacy was similar to the efficacy in paediatric patients above one year of age, given the same dose per kilogram (2 mg/kg), when assessed as the proportion of patients with postoperative pain, time to first pain and time to treatment with supplementary analgesics.

In two studies in patients 1 day to 12 years old an epidural bolus was followed by a continuous infusion for up to 72 hours. The epidural bolus volume ranged between 0.5 and 1 mL/kg of ropivacaine 2 mg/mL (0.2%), with lower volumes given for thoracic than for lumbar injections. The infusion rate was 0.2 mg/kg/h in neonates and infants below 6 months of age and 0.4 mg/kg/h of ropivacaine 2 mg/mL (0.2%) in patients above 6 months of age. More than 80% of the patients had no/mild pain, or were asleep, at any time point. There was no difference in pain score between the 0 to 6 months group (ropivacaine 0.2 mg/kg/h infusion) and the 6 to 12 months group (ropivacaine 0.4 mg/kg/h infusion). The median time to supplementary analgesia was 3.3 hours in patients older than 1 year, whereas in younger patients less than 40% had been given supplementary analgesia after 72 hours. Motor block was observed in 32% of the patients above 1 year of age but in none of the infants below 1 year of age. Ropivacaine was well tolerated in all paediatric age groups.

INDICATIONS

Surgical anaesthesia (Adults and children over 12 years of age)

- epidural block for surgery including caesarean section.
- field block (minor nerve block and infiltration).
- major nerve block.

Analgesia (Adults and children over 12 years of age)

- continuous epidural infusion or intermittent bolus epidural administration for analgesia in postoperative pain or labour pain
- field block (minor nerve block and infiltration).
- continuous peripheral nerve block infusion or intermittent injections for post operative pain management

There are no safety or efficacy data to support the use of NAROPIN administered epidurally for analgesia for longer than 72 hours. Data for peripheral nerve block administered as a continuous peripheral infusion or intermittent injections support the use for up to 48 hours only.

Analgesia (Children aged 0 - 12 years)

For peri- and post-operative pain management

- Caudal epidural block in neonates (> 37 weeks gestation and over 2500 g weight), infants and children up to and including 12 years
- Continuous epidural infusion in infants (> 30 days and over 2500 g weight) and children up to and including 12 years

There are no safety or efficacy data to support the use of NAROPIN administered epidurally for analgesia for longer than 72 hours.

CONTRAINDICATIONS

1. Allergy or hypersensitivity to amide type local anaesthetics. Detection of suspected hypersensitivity by skin testing is of limited value.
2. Intravenous administration.
3. Local anaesthetics are contraindicated for epidural and spinal anaesthesia in patients with uncorrected hypotension.
4. Local anaesthetic techniques must not be used when there is inflammation and/or sepsis in the region of the proposed injection and/or in the presence of septicaemia.
5. Intravenous regional anaesthesia (Bier's block) as unintentional passage of local anaesthetic into the systemic circulation, despite the use of a tourniquet, may cause systemic toxic reactions.
6. The use of ropivacaine is not recommended for obstetric paracervical block.
7. General contraindications related to epidural anaesthesia, regardless of the local anaesthetic used, should be taken into account.

PRECAUTIONS

1. WHEN ANY LOCAL ANAESTHETIC AGENT IS USED, RESUSCITATIVE EQUIPMENT AND DRUGS, INCLUDING OXYGEN, SHOULD BE IMMEDIATELY AVAILABLE IN ORDER TO MANAGE POSSIBLE ADVERSE REACTIONS INVOLVING THE CARDIOVASCULAR, RESPIRATORY OR CENTRAL NERVOUS SYSTEMS. BECAUSE OF THE POSSIBILITY OF HYPOTENSION AND BRADYCARDIA FOLLOWING MAJOR BLOCKS, AN IV CANNULA SHOULD BE INSERTED BEFORE THE LOCAL ANAESTHETIC IS INJECTED.
2. INJECTION SHOULD ALWAYS BE MADE SLOWLY WITH FREQUENT ASPIRATIONS TO AVOID INADVERTENT INTRAVASCULAR INJECTION WHICH CAN PRODUCE TOXIC EFFECTS.
3. ALTHOUGH INTRA-ARTICULAR CONTINUOUS INFUSIONS OF LOCAL ANAESTHETICS FOLLOWING ARTHROSCOPIC AND OTHER SURGICAL PROCEDURES IS AN UNAPPROVED USE, THERE HAVE BEEN POST-MARKETING REPORTS OF CHONDROLYSIS IN PATIENTS RECEIVING SUCH INFUSIONS. THE MAJORITY OF REPORTED CASES OF CHONDROLYSIS HAVE INVOLVED THE SHOULDER JOINT; CASES OF GLENO-HUMERAL CHONDROLYSIS HAVE BEEN DESCRIBED IN PAEDIATRIC AND ADULT PATIENTS FOLLOWING INTRA-ARTICULAR CONTINUOUS INFUSIONS OF LOCAL ANAESTHETICS WITH AND WITHOUT ADRENALINE FOR PERIODS OF 48 TO 72 HOURS. THERE IS INSUFFICIENT INFORMATION TO DETERMINE WHETHER SHORTER INFUSION PERIODS ARE NOT ASSOCIATED WITH THESE FINDINGS. 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 SECOND MONTH AFTER SURGERY. CURRENTLY, THERE IS NO EFFECTIVE TREATMENT FOR CHONDROLYSIS; PATIENTS WHO EXPERIENCED CHONDROLYSIS HAVE REQUIRED ADDITIONAL DIAGNOSTIC AND THERAPEUTIC PROCEDURES AND SOME REQUIRED ARTHROPLASTY OR SHOULDER REPLACEMENT. THEREFORE, NAROPIN SHOULD NOT BE USED FOR POST-OPERATIVE INTRA-ARTICULAR CONTINUOUS INFUSION.
4. LOW MOLECULAR WEIGHT HEPARINS AND HEPARINOIDS (Spinal/Epidural Haematomas) – When neuraxial anaesthesia (epidural / spinal anaesthesia) is employed, patients anti-coagulated or scheduled to be anti-coagulated with low molecular weight heparins or heparinoids are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events is increased by the use of indwelling epidural catheters, traumatic or repeated epidural/spinal puncture, and the concomitant use of drugs affecting haemostasis such as NSAIDs, platelet inhibitors or other anticoagulants. Patients should be frequently monitored for signs and symptoms of neurological impairment.
5. The safety and efficacy of NAROPIN depends on proper dosage, correct technique and adequate precautions. Standard textbooks should be consulted regarding specific techniques and precautions for various regional anaesthetic procedures.
6. The lowest dosage that results in efficacious anaesthesia should be used (see DOSAGE AND ADMINISTRATION).

   Elderly, young or debilitated patients, including those with partial or complete heart conduction block, advanced liver disease or severe renal dysfunction, should be given reduced doses commensurate with their age and physical condition.

   Children aged between 0 and 12 years should be given doses commensurate with their weight and clinical status.
7. Ropivacaine is eliminated primarily by hepatic metabolism and changes in hepatic function may have significant consequences. Ropivacaine has an intermediate to low clearance, which depends on its unbound fraction and intrinsic metabolic clearance. Ropivacaine should therefore be used with caution in patients with severe hepatic disease.
8. 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 dysfunction may increase the risk of systemic toxicity (see DOSAGE AND ADMINISTRATION).
9. The possibility of hypotension and bradycardia following epidural blockade should be anticipated and precautions taken, including the prior establishment of an intravenous line and the availability of vasopressor drugs, vagolytic drugs and oxygen.
10. Certain local anaesthetic procedures such as injection in the head and neck region, including retrobulbar, dental and stellate ganglion blocks, may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used. The side effects may be similar to the systemic toxicity seen with unintentional intravascular injections of larger doses.
11. Ropivacaine should be used with caution in patients with known drug sensitivities.
12. Careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness should be accomplished after each local anaesthetic injection. It should be kept in mind that at such times restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of CNS toxicity.
13. Local anaesthetics should be given with great caution (if at all) to patients with pre-existing abnormal neurological pathology, e.g. myasthenia gravis. Use with extreme caution in epidural, caudal and spinal anaesthesia when there are serious diseases of the CNS or of the spinal cord, e.g. meningitis, spinal fluid block, cranial or spinal haemorrhage, tumours, poliomyelitis, syphilis, tuberculosis or metastatic lesions of the spinal cord.

PHARMA CODE NO. 7511

Text area for artwork

ASPEN Artwork Panel

AW Version: 02	**Page:** 1 of 2
New Item Code: PS15765	
Replacement: PS05700	
Market: SG	
Product Name: Naropin	
Number of Colours: 1	
BLACK	
Manufacturing Site: Södertälje	
Drawing Ref. Number: AZL039A	
Drawing Version: N/A	
Originated by: Mateusz Zielinski	
Originated at: Perigord AS	
Originated on: 28 Sep 2018	
Amended on: 24 Oct 2018	

160 mm Measuring Bar

ASPEN Artwork Panel • May 2013 • Version 5

14. Major peripheral nerve blocks may involve the administration of a large volume of local anaesthetic in highly vascularised areas, often close to large vessels where there is an increased risk of intravascular injection and/or rapid systemic absorption. This can lead to high plasma concentrations.
15. If NAROPIN is administered simultaneously by two or more different routes, the total dose and hence the risk of systemic toxicity should be considered.
16. Patients treated with class III anti-arrhythmic drugs (e.g. amiodarone) should be under close surveillance. ECG monitoring should also be considered, since cardiac effects may be additive.
17. 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.
18. Neonates need special attention due to immaturity of some organs and functions. This is especially important during continuous epidural infusion. If epidural infusions are to be used in neonates, ropivacaine doses must be individually titrated by a specialist in paediatric anaesthesia. Regular monitoring for systemic toxicity (e.g. by signs of CNS toxicity, ECG, SpO_2) is always required for neonates. Monitoring should be continued after completion of infusion due to decreased rates of elimination of ropivacaine in neonates. Dose recommendations have not been established in premature neonates but organ immaturity would be expected to result in even slower elimination.
19. Naropin is possibly porphyrinogenic 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.
20. Epidural and intrathecal anaesthesia may lead to hypotension and bradycardia. The risk of such effects can be reduced, eg, by injecting a vasopressor. Hypotension should be treated promptly with a sympathomimetic intravenously, repeated as necessary.

Genotoxicity
Ropivacaine hydrochloride was negative in the Ames salmonella/mammalian microsome mutagenicity test, human lymphocyte chromosome aberration test, mouse micronucleus test, E. coli differential DNA repair test, E. coli host-mediated DNA repair test in mice, and the somatic mutation and recombination test in Drosophila melanogaster (fruit fly), and weakly mutagenic in the mouse lymphoma test. The clinical use of ropivacaine is unlikely to pose any risk of genotoxicity.

Carcinogenicity
Long term animal assays of carcinogenic potential have not been performed.

Effects on fertility
No adverse effects on fertility and reproductive performance were seen in rats over 2 generations following daily subcutaneous administration of ropivacaine from prior to mating through weaning, with estimated systemic exposure (plasma AUC) twice the clinical exposure following a 200 mg epidural dose. Increased pup loss in the first 3 days post partum was attributed to reduced maternal care.

Effects on ability to drive and use machines
Depending on the dose, local anaesthetics may have a mild effect on mental function and coordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness. Patients should be warned of this possibility and advised not to drive a motor vehicle or operate machinery if affected.

USE IN PREGNANCY Category B1
There was no evidence of teratogenicity following daily subcutaneous administration of ropivacaine to rats and rabbits during the period of organogenesis, with estimated systemic exposure (plasma AUC) twice the clinical exposure following a 200 mg epidural dose. In rats treated similarly with ropivacaine daily from late gestation to weaning, there were no treatment-related effects on late foetal development, parturition, lactation, neonatal viability, or offspring growth. In rats treated from late gestation to weaning, maternal toxicity was elicited at a lower dose and lower unbound plasma concentration with bupivacaine than with ropivacaine.

There are no clinical studies in pre-term pregnant women on the effects of NAROPIN on the developing foetus. NAROPIN should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

The epidural use of NAROPIN in obstetrics is well documented and adverse effects have been reported (see ADVERSE EFFECTS: FOETAL, NEONATAL AND INFANT ADVERSE EVENTS).

Use in lactation
Subcutaneous administration of ropivacaine to rats from late gestation to weaning, with estimated systemic exposure (plasma AUC) twice the clinical exposure following a 200 mg epidural dose, did not effect late foetal development, parturition, lactation, neonatal viability, or offspring growth. Ropivacaine and/or its metabolites are excreted into milk in rats, but excretion into human milk has not been investigated.

INTERACTIONS WITH OTHER MEDICINES

Local anaesthetics and Antiarrhythmic Drugs
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. Specific interaction studies with NAROPIN and class III anti-arrhythmic drugs (e.g. amiodarone) have not been performed, but caution is advised (see Precaution 16).

Adrenaline
The duration and intensity of ropivacaine sensory block is not improved by the addition of adrenaline.

Alkaline solutions
The solubility of ropivacaine is limited at pH values above 6.0. This must be taken into consideration if adding an alkaline solution since precipitation might occur at higher pH values.

Cytochrome P450 Interactions (see Pharmacokinetics)
Ropivacaine is metabolised by the enzymes CYP1A2 and CYP3A4. Interactions with inducers of these enzymes are not expected to be clinically relevant, however there is a potential for metabolic interaction when NAROPIN is used in combination with a potent enzyme inhibitor.

CYP1A2 Inhibitors
Fluvoxamine
Oral fluvoxamine treatment caused a 70% decrease in ropivacaine clearance and a 3-fold higher AUC in healthy volunteers. Single administrations of ropivacaine should be used with care in patients who are concomitantly receiving a potent CYP1A2 inhibitor. Repeated administration or long term infusion should be avoided in such patients.

A theoretical possibility of metabolic drug interactions with potent inhibitors of CYP1A2, such as enoxacin, may exist.

CYP3A4 Inhibitors
Ketoconazole
Co-administration with ketoconazole, a potent inhibitor of CYP3A4, has been shown to cause a marginal (15%) decrease in ropivacaine clearance in healthy volunteers.

Theoretical Interactions
Cimetidine, an inhibitor of CYP2E1, did not inhibit the formation of 3-hydroxy-ropivacaine but inhibited some formation of minor metabolites *in vitro*.

Metabolic Interactions
With the low to intermediate hepatic extraction ratio of ropivacaine (mean 0.4), a fall in the liver blood flow is not expected to have a significant influence on ropivacaine clearance (see PRECAUTION 6).

Clinical relevance of interactions
In the clinical experience with ropivacaine, patients usually received NAROPIN in combination with several other therapies. The safety evaluation of NAROPIN is therefore based upon its use in combination with various concomitant treatments. The review of safety data in these studies show that NAROPIN has a safety profile comparable to other amide local anaesthetics used for regional anaesthesia.

These data did not indicate any specific drug interactions that would require special study for the use of ropivacaine as a single-dose or for treatment for less than 24 hours. Furthermore, drugs metabolised by CYP1A2, e.g. paracetamol, have also been used in combination with ropivacaine in the clinical programme, without clinical evidence of metabolic interactions (see Pharmacokinetics).

ADVERSE EFFECTS
Adverse events reported in association with NAROPIN are similar in character to those observed with other local anaesthetics of the amide type.

Adverse reactions may be due to high plasma levels as a result of excessive dosage, rapid absorption, delayed elimination or metabolism, or inadvertent intravascular injection. They should be distinguished from the physiological effects of the nerve block itself e.g. a decrease in blood pressure and bradycardia during epidural and events caused by needle puncture (e.g. spinal haematoma, postdural puncture, headache, meningitis and epidural abscess).

Pronounced acidosis, hyperkalaemia or hypoxia in the patient may increase the risk and severity of toxic reactions.

The effects of systemic overdose and unintentional intravascular injection may involve the central nervous system and/or the cardiovascular system (see OVERDOSAGE). Inadvertent subarachnoid injection may lead to CNS depression, respiratory arrest and cardiovascular collapse.

Very common events (>10%)

Cardiovascular: Hypotension[c]

Gastrointestinal: Nausea

Common events (>1%)
A large number of adverse events have been reported during clinical development, the majority related to the expected effects of the block and to the clinical situation rather than reactions to the drug. Thus hypotension and nausea have been registered in 39% and 25%, respectively, of the patients treated in clinical studies.

The following adverse events are considered to be of clinical importance regardless of causal relationship.

Cardiovascular: Bradycardia[a], hypertension and tachycardia.

Nervous system: Paraesthesia, temperature elevation, rigors (chills), headache[a] and dizziness.

Gastrointestinal: Vomiting[a,d].

Other: Urinary retention[a], back pain, insomnia, chest pain, pain and oliguria.

Uncommon events (≤1%)
Acute systemic toxicity: More serious but less common reactions that reflect acute systemic toxicity[b], include dysarthria, muscular rigidity, muscle twitching, unconsciousness, convulsions, hypoxia, hypercapnia, apnoea, severe hypotension, bradycardia, arrhythmias and cardiac arrest. Indirect cardiovascular effects (hypotension, bradycardia) may occur after epidural administration, depending on the extent of the concomitant sympathetic block.

Convulsions, grand mal convulsions and seizures have been observed following unintended intravascular injection of NAROPIN.

Due to the low doses used for intrathecal anaesthesia, the potential for systemic toxic reactions is expected to be low.

Psychiatric: Anxiety

Nervous System: Hypoaesthesia[a]

Vascular: Syncope[a]

Respiratory, thoracic and mediastinal: Dyspnoea[a]

General disorders and administration site conditions: Hypothermia[a]

Rare (≤0.1%)
Cardiac disorders: Cardiac arrest, cardiac arrhythmias

General disorders and administration site conditions: Allergic reactions (anaphylactoid 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 dysfunctions (eg, 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.

Fetal, 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 events (>1%)
Cardiovascular: Fetal distress, fetal tachycardia and fetal bradycardia.

Gastrointestinal: Neonatal vomiting.

Respiratory: Neonatal respiratory disorders and neonatal tachypnoea.

Other: Neonatal fever and neonatal jaundice.

Uncommon events (<1%)
Metabolic: Fetal acidosis and neonatal hypoglycaemia.

Other: Hypotonia, neonatal sepsis and low Apgar score.

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

The presentations of NAROPIN injection solutions are intended for single use only. Any solution remaining from an opened container should be discarded.

The lowest dosage that results in effective anaesthesia should be used and should be based on the status of the patient and the type of regional anaesthesia intended. In general, surgical anaesthesia requires the use of higher concentrations and doses than those required for analgesia.

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

Adults and children above 12 years of age
RECOMMENDED DOSAGES FOR NAROPIN SOLUTION FOR VARIOUS ANAESTHETIC PROCEDURES IN THE AVERAGE, HEALTHY, 70KG ADULT PATIENT.

	%	Conc. (mg/mL)	Volume mL	Dose mg
SURGICAL ANAESTHESIA				
Lumbar Epidural Administration				
Abdominal, pelvic and lower limb surgery	0.75% 1%	7.5 10.0	15 - 25 15 - 20	113 - 188 150 - 200
Caesarean Section	0.75%	7.5	15 - 20	113 - 150
Thoracic Epidural Administration				
Upper abdominal and thoracic surgery	0.75%	7.5	5 - 15	38 - 113
Field Block (incl. minor nerve blocks and infiltration)	0.75%	7.5	1 - 25	7.5 - 188
Major Nerve Block	0.75%	7.5	10 - 40	75 - 300[(1)]
ANALGESIA				
Lumbar Epidural Administration				
Bolus	0.2%	2.0	10 - 20	20 - 40
Intermittent injections (top-up) (e.g.) labour pain management	0.2%	2.0	10 - 15 (minimum interval 30 minutes)	20 - 30
Continuous infusion (incl. labour pain and postoperative pain management)	0.2%	2.0	6 - 14 mL/h	12 - 28 mg/h
Thoracic Epidural Administration Continuous infusion for postoperative pain management	0.2%	2.0	6 – 14 mL/h	12 - 28 mg/h
Field Block (incl. minor nerve blocks and infiltration)	0.2%	2.0	1 - 100	2 - 200
Peripheral Nerve Block (Femoral or interscalene block) Continuous infusion or intermittent injections for postoperative pain management)	0.2%	2.0	5 - 10 mL/h	10 - 20 mg/h[(2)]

(1) For major nerve blocks the dosage should be adjusted to the site of administration and patient status. Interscalene and supraclavicular brachial plexus blocks may be associated with higher frequency of serious adverse reactions regardless of the local anaesthetic used.
(2) Up to 48 hours only usage

The appropriate concentration and volume for each procedure should be selected. The 1% (10 mg/mL) formulation is recommended for epidural anaesthesia in which a profound motor block is essential for surgery. There is no information available regarding the use of concentrations above 0.75% (7.5 mg/mL) for caesarean section. For further details of procedures please see current standard textbooks.

NOTE
Careful aspiration before and during injection is recommended to avoid intravascular injection.

1. **Test Dose**
For epidural anaesthesia, or when a large dose is to be injected, a 3 - 5 mL test dose of a local anaesthetic solution, preferably containing 5 µg/mL of adrenaline (e.g. 3 mL of Xylocaine® 2.0% with adrenaline 1:200,000) should be administered. Verbal contact and repeated monitoring of heart rate and blood pressure should be maintained for 5 minutes following the test dose after which, in the absence of signs of subarachnoid, intravascular or intrathecal injection, the main dose may be administered.

An inadvertent intravascular injection may be recognised by a temporary increase in heart rate and an accidental intrathecal injection by signs of a spinal block.

Prior to and during administration of the total dose, aspiration should be repeated. The main dose should be injected **slowly** at a rate of 25 - 50 mg/min, while closely observing the patient's vital functions and maintaining verbal contact. If toxic symptoms or signs occur, the injection should be stopped immediately.

2. **Analgesia**
When calculating the dosage for postoperative analgesia, the use of intraoperative local anaesthetic/s should be taken into account. For treatment of postoperative pain, the following technique can be recommended:

Epidural analgesia is maintained with NAROPIN 0.2% (2 mg/mL) infusion. Infusion rates of 6 - 14 mL (12 - 28mg) 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 experience supports the use of NAROPIN 0.2% (2 mg/mL) epidural infusions for up to 72 hours. Data for peripheral nerve block administered as a continuous peripheral infusion or intermittent injections support the use for up to 48 hours only at dosages of 10 – 20 mg/hr (5 – 10mL/hr).

When prolonged epidural blocks are used, either by continuous infusion or repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. Cumulative doses of 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.

When prolonged peripheral nerve blocks are applied, either through continuous infusion or through repeated injections, the risk of reaching a toxic plasma concentration or inducing local neural injury must be considered.

In clinical studies, femoral nerve block was established with 300 mg NAROPIN 0.75% (7.5 mg/mL) and interscalene block with 225 mg NAROPIN 0.75% (7.5 mg/mL), respectively, before surgery. Analgesia was then maintained with NAROPIN 0.2% (2 mg/mL). Infusion rates or intermittent injections of 10 - 20 mg per hour for 48 hours provided adequate analgesia and were well tolerated.

Use in Children

Dosage Recommendations for Paediatric Patients 0 up to and including 12 Years of Age

	%	Conc (mg/mL)	Volume (mL/kg)	Dose (mg/kg)
ANALGESIA				
Caudal Epidural Administration (0 - 12 years) Blocks below T12, in children with body weight 2.5kg to 25kg	0.2%	2.0	1	2
Continuous Epidural Infusion (31 days- 12 years) In children with body weight 2.5 kg to 25 kg				
31 days up to 6 months				
Bolus dose[a]	0.2%	2.0	0.5-1	1-2
Infusion up to 72 hours	0.2%	2.0	0.1 mL/kg/h	0.2 mg/kg/h
6 to 12 months				
Bolus dose[a]	0.2%	2.0	0.5-1	1-2
Infusion up to 72 hours	0.2%	2.0	0.2 mL/kg/h	0.4 mg/kg/h
1 to 12 years				
Bolus dose[b]	0.2%	2.0	1	2
Infusion up to 72 hours	0.2%	2.0	0.2 mL/kg/h	0.4mg/kg/h

a Doses in the low end of the dose interval are recommended for thoracic epidural blocks while doses in the high end are recommended for lumbar or caudal epidural blocks.
b Recommended for lumbar epidural blocks. It is good practice to reduce the bolus dose for thoracic epidural analgesia.

The doses in the table should be regarded as guidelines for use in paediatrics. Individual variations occur. In children with a high body weight a gradual reduction of the dosage is often necessary and should be based on the ideal body weight. The volume for single caudal epidural block and the volume for epidural bolus doses should not exceed 25 mL in any patient. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

Careful aspiration before and during injection is recommended to prevent intravascular injection. The patient's vital functions should be observed closely during the injection. If toxic symptoms occur, the injection should be stopped immediately.

A single caudal epidural injection of NAROPIN 0.2% (2 mg/mL) produces adequate postoperative analgesia below T12 in the majority of patients when a dose of 2 mg/kg is used in a volume of 1 mL/kg. In children above 4 years of age, doses up to 3 mg/kg have been used safely by the caudal route. The safety and efficacy of doses above 3 mg/kg have not been demonstrated and therefore cannot be recommended. The volume of the caudal epidural injection may be adjusted to achieve a different distribution to sensory block, as recommended in standard textbooks.

Fractionation of the calculated local anaesthetic dose is recommended, whatever the route of administration.

The use of NAROPIN in premature children has not been documented.

Use in Debilitated or Elderly Patients
Debilitated or elderly patients, including those with partial or complete heart conduction block, advanced liver disease or severe renal dysfunction should be given reduced dosage commensurate with their physical condition. Clinical studies with this group of patients have not been performed (see PRECAUTIONS).

OVERDOSAGE
Acute emergencies associated with the use of local anaesthetics are generally related to high plasma levels or to unintended subarachnoid injection of the local anaesthetic solution (see ADVERSE EFFECTS and PRECAUTIONS).

Accidental intravascular injections of local anaesthetics may cause immediate toxic effects. Toxic effects may also arise from exceptionally rapid absorption from highly vascularised areas. In the event of overdose, peak plasma concentrations may not be reached for one to two hours, depending on the site of the injection and signs of toxicity may thus be delayed. Systemic toxic reactions may involve the central nervous system and the cardiovascular system.

In children, as in adults, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during deep sedation or general anaesthesia.

Symptoms
Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. Initially symptoms such as visual or hearing disturbances, perioral numbness, dizziness, light headedness, tingling and paraesthesia are seen. Dysarthria, muscular rigidity and muscular twitching are more serious and may precede the onset of generalised convulsions.

Unconsciousness and grand mal convulsions may follow, which can last from a few seconds to several minutes. Hypoxia and hypercapnia occur rapidly during convulsions due to the increased muscular activity, together with disruption to respiration and possible loss of functional airways. In severe cases apnoea may occur. Respiratory and metabolic acidosis, hyperkalaemia, hypocalcaemia and hypoxia 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 should be rapid unless large amounts of the drug have been injected.

Cardiovascular toxicity indicates a more severe situation. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics. In volunteers the intravenous infusion of ropivacaine resulted in signs of depression of conductivity and contractility.

Cardiovascular toxic effects are 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. However in rare cases, cardiac arrest has occurred without prodromal CNS effects.

Treatment
If signs of acute systemic toxicity or total spinal block occur, injection of the local anaesthetic should be stopped immediately.

Treatment consists of ensuring adequate ventilation and arresting convulsions. Assisted or controlled ventilation should be maintained with oxygen, if required.

If convulsions occur and do not spontaneously stop within 15 - 20 seconds, an anticonvulsant should be given intravenously e.g. diazepam 5 - 10 mg IV or where indicated, sodium thiopentone (5 mg/kg). If convulsions interfere with breathing and/or are not rapidly controlled by specific anticonvulsant medication, suxamethonium (1 - 2 mg/kg) may be used to paralyse the patient. Artificial ventilation must then be instituted.

If cardiovascular depression is evident (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor and or inotropic agents should be considered.

If ventricular fibrillation, cardiac arrest or circulatory arrest occur, cardiopulmonary resuscitation must be instituted and maintained. 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.

COMPATIBILITY AND ADMIXTURES
NAROPIN solution for infusion in plastic infusion bags (Polybag) is chemically and physically compatible with fentanyl citrate, morphine sulphate and clonidine hydrochloride.

Concentration of NAROPIN: 0.1 - 0.2% (1 - 2 mg/mL)	
Additive	Concentration
Fentanyl citrate	1.0 - 10.0 microgram/mL
Morphine sulphate	20.0 - 100.0 microgram/mL
Clonidine hydrochloride	5.0 - 50.0 microgram/mL

Chemical and physical stability of these mixtures have been demonstrated for 30 days at up to 30°C. To reduce microbiological hazard, these admixtures should be used immediately. If not used immediately, store at 2 - 8°C for not more than 24 hours.

PRESENTATIONS AND STORAGE CONDITIONS
Naropin 0.2% (2.0 mg/mL)
100 mL, 200 mL Polybag infusion bags

Naropin 1% (10.0 mg/mL)
10 mL, 20 mL Polyamp DuoFit ampoules

NAROPIN Polybag and Polyamp DuoFit presentations are in a Sterile Theatre Pack.

NAROPIN Polyamp presentations must be stored below 30°C. Do not freeze.

NAROPIN Polybag presentations must be stored below 30°C. Do not freeze.

Polybag and Polyamp must not be re-autoclaved.

NAME AND ADDRESS OF PRODUCT OWNER
Aspen Global Incorporated
GBS Plaza
Grand Bay, Mauritius

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aspen

ASPEN Artwork Panel

AW Version: 02	**Page:** 2 of 2
New Item Code: PS15765	
Replacement: PS05700	
Market: SG	
Product Name: Naropin	
Number of Colours: 1	
BLACK	
Manufacturing Site: Södertälje	
Drawing Ref. Number: AZL039A	
Drawing Version: N/A	
Originated by: Mateusz Zielinski	
Originated at: Perigord AS	
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160 mm Measuring Bar

ASPEN Artwork Panel • May 2013 • Version 5