

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naropin 2 mg/ml solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for infusion contains ropivacaine hydrochloride monohydrate equivalent to 2 mg ropivacaine hydrochloride.

1 bag of 100 ml or 200 ml solution for infusion contains ropivacaine hydrochloride monohydrate equivalent to 200 mg and 400 mg ropivacaine hydrochloride respectively.

For excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for infusion for perineural and epidural administration (100 and 200 ml)
Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Naropin is indicated for:

1. Surgical anaesthesia:
Epidural blocks for surgery, including Caesarean section
Major nerve blocks
Field blocks
2. Acute pain management:
Continuous epidural infusion or intermittent bolus administration during postoperative or labour pain
Field blocks
Continuous peripheral nerve block via a continuous infusion or intermittent bolus injections, e.g. postoperative pain management
3. Acute pain management in paediatrics:
(pre- and postoperative)
Caudal epidural block in neonates, infants and children up to and including 12 years
Continuous epidural infusion in neonates, infants and children up to and including 12 years

4.2 Posology and method of administration

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

Posology

Adults and children above 12 years of age

The following table is a guide to dosage for the more commonly used blocks. The smallest dose required to produce an effective block should be used. The clinician's experience and knowledge of the patient's physical status are of

importance when deciding the dose.

Table 1 Adults and children above 12 years of age

	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
	10.0	15-20	150-200	10-20	4-6
Caesarean Section	7.5	15-20	113-150 ¹⁾	10-20	3-5
Thoracic Epidural Administration					
To establish block for post-operative pain relief	7.5	5-15 (depen- dent on the level of injection)	38-113	10-20	n/a ²⁾
Major Nerve Block*					
Brachial plexus block	7.5	30-40	225-300 ³⁾	10-25	6-10
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 (mini-mum interval 30 minutes)	20-30		
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 (postoperative pain management)	2.0	6-14 ml/h	12-28 mg/h	n/a	n/a
Field Block (e.g. minor nerve blocks and infiltration)	2.0	1-100	2.0-200	1-5	2-6
Peripheral nerve block (Femoral or interscalene block)					
Continuous infusion or intermittent injections (e.g. postoperative pain management)	2.0	5-10 ml/h	10-20 mg/h	n/a	n/a

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 in the column 'Dose' reflect the expected average dose range needed. Standard textbooks should be consulted for both factors affecting specific

block techniques and individual patient requirements.

* With regard to major nerve block, only for brachial plexus block a dose recommendation can be given. For other major nerve blocks lower doses may be required. However, there is presently no experience of specific dose recommendations for other blocks.

1) Incremental dosing should be applied, the starting dose about 100 mg (97,5 mg = 13 ml; 105 mg = 14 ml) to be given over 3-5 minutes. Two extra doses, in total an additional 50 mg, may be administered as needed.

2) n/a = not applicable

3) 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 section 4.4 Special warnings and special precautions for use*).

In general, surgical anaesthesia (e.g. epidural administration) requires the use of the higher concentrations and doses. The Naropin 10 mg/ml formulation is recommended for epidural anesthesia in which a complete motor block is essential for the surgery. For analgesia (e.g. epidural administration for acute pain management) the lower concentrations and doses are recommended.

Method of administration

Careful aspiration before and during injection is recommended to prevent intravascular injection. When a large dose is to be injected, a test dose of 3-5 ml lidocaine (lignocaine) with adrenaline (epinephrine) (Xylocaine® 2% with Adrenaline (epinephrine) 1:200.000) is recommended. 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.

Aspiration should be performed prior to and during administration of the main dose, which should be injected slowly or in incremental doses, at a rate of 25-50 mg/min, while closely observing the patient's vital functions and maintaining verbal contact. If toxic symptoms occur, the injection should be stopped immediately.

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

In brachial plexus block a single dose of 300 mg has been used in a limited number of patients and was well tolerated.

When prolonged blocks are used, either through continuous infusion or through repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. Cumulative doses up to 675 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. In a limited number of patients higher doses of up to 800 mg/day have been administered with relatively few adverse reactions.

For 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. 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. The maximum duration of epidural block is 3 days. However, close monitoring of analgesic effect should be performed in order to remove the catheter as soon as the pain condition allows it. 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. The combination of Naropin and fentanyl provided improved pain relief but caused opioid side effects. The combination of Naropin and fentanyl has been investigated only for Naropin 2 mg/ml.

When prolonged peripheral nerve blocks are applied, either through continuous infusion or through repeated injections, the risks 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 7.5 mg/ml and interscalene block with 225 mg Naropin 7.5 mg/ml, respectively, before surgery. Analgesia was then maintained with Naropin 2 mg/ml. Infusion rates or intermittent injections of 10-20 mg per hour for 48 hours provided adequate analgesia and were well tolerated.

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

Table 2 Paediatric patients 0 up to and including 12 years of age

	Conc. mg/ml	Volume ml/kg	Dose mg/kg
ACUTE PAIN MANAGEMENT			
(per- and postoperative)			
Single Caudal Epidural Block	2.0	1	2
Blocks below T12, in children with a body weight up to 25 kg			
Continuous Epidural Infusion			
In children with a body weight up to 25 kg			
<i>0 up to 6 months</i>			
Bolus dose ^a	2.0	0.5-1	1-2
Infusion up to 72 hours	2.0	0.1 mL/kg/h	0.2 mg/kg/h
<i>6 up to 12 months</i>			
Bolus dose ^a	2.0	0.5-1	1-2
Infusion up to 72 hours	2.0	0.2 mL/kg/h	0.4 mg/kg/h
<i>1 to 12 years</i>			
Bolus dose ^b	2.0	1	2
Infusion up to 72 hours	2.0	0.2 mL/kg/h	0.4 mg/kg/h

The dose 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.

- 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

Method of administration

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 ropivacaine 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. The volume of the caudal epidural injection may be adjusted to achieve a different distribution of sensory block, as recommended in standard textbooks. In children above 4 years of age, doses up to 3 mg/kg of a concentration of ropivacaine 3 mg/ml have been studied. However, this concentration is associated with a higher incidence of motor block.

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

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

4.3 Contraindications

Hypersensitivity to ropivacaine or to other local anaesthetics of the amide type.
General contra-indications related to epidural anesthesia, regardless of the local anaesthetic used, should be taken into

account.
 Intravenous regional anaesthesia.
 Obstetric paracervical anaesthesia
 Hypovolaemia

4.4 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 intravenous line inserted before the blocking procedure.

The clinician responsible should take the necessary precautions to avoid intravascular injection (*see section 4.2 Posology and method of administration*) and be appropriately trained and familiar with diagnosis and treatment of side effects, systemic toxicity and other complications (*see section 4.8 Undesirable effects and 4.9 Overdose*) 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.

Caution is required to prevent injections in inflamed areas.

Cardiovascular

Patients treated with anti-arrhythmic drugs class III (eg, 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.

Head and neck blocks

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.

Major peripheral nerve blocksMajor 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.

Hypersensitivity

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

Hypovolaemia

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

Patients in poor general health

Patients in poor general condition due to ageing 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.

Patients with hepatic and renal impairment

Ropivacaine is metabolised in the liver and should therefore be used with caution in patients with severe liver disease; 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.

Acute porphyria

Naropin[®] solution for injection and infusion 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, according to standard textbooks and/or in consultation with disease area experts.

Excipients with recognised action/effect

This medicinal product contains maximum 3.7 mg sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

Prolonged administration

Prolonged administration of ropivacaine should be avoided in patients concomitantly treated with strong CYP1A2 inhibitors, such as fluvoxamine and enoxacin, *see section 4.5*.

Paediatric patients

Neonates may need special attention due to immaturity of metabolic pathways. The larger variations in plasma concentrations of ropivacaine observed in clinical trials in neonates suggest that there may be an increased risk of systemic toxicity in this age group, especially during continuous epidural infusion. The recommended doses in neonates are based on limited clinical data. When ropivacaine is used in this patient group, regular monitoring of systemic toxicity (e.g. by signs of CNS toxicity, ECG, SpO₂) and local neurotoxicity (e.g. prolonged recovery) is required, which should be continued after ending infusion, due to a slow elimination in neonates.

4.5 Interaction with other medicinal products 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, e.g. certain antiarrhythmics, such as lidocaine and mexiletine, since the systemic toxic effects are additive. Simultaneous use of Naropin with general anaesthetics or opioids may potentiate each others (adverse) effects. Specific interaction studies with ropivacaine and anti-arrhythmic drugs class III (eg, amiodarone) have not been performed, but caution is advised (*see also section 4.4 Special warnings and precautions for use*).

Cytochrome P450 (CYP) 1A2 is involved in the formation of 3-hydroxy ropivacaine, the major metabolite. In vivo the plasma clearance of ropivacaine was reduced by up to 77% during coadministration of fluvoxamine, a selective and potent CYP1A2 inhibitor. Thus strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin, given concomitantly during prolonged administration of Naropin, can interact with Naropin. Prolonged administration of ropivacaine should be avoided in patients concomitantly treated with strong CYP1A2 inhibitors, *see also section 4.4*.

In vivo the plasma clearance of ropivacaine was reduced by 15% during coadministration of ketoconazole, a selective and potent inhibitor of CYP3A4. However the inhibition of this isozyme is not likely to have clinical relevance.

In vitro ropivacaine is a competitive inhibitor of CYP2D6 but does not seem to inhibit this isozyme at clinically attained plasma concentrations.

4.6 Pregnancy and lactation**Pregnancy**

Apart from epidural administration for obstetrical use, there are no adequate data on the use of ropivacaine in human pregnancy. Experimental animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fœtal development, parturition or postnatal development (*see section 5.3 Preclinical safety data*).

Lactation

There is no data available concerning the excretion of ropivacaine into human milk.

4.7 Effects on ability to drive and use machines

No data is available. Depending on the dose, local anaesthetics may have a minor influence on mental function and co-

ordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

General

The adverse reaction profile for Naropin is similar to those for other long acting local anaesthetics of the amide type. Adverse drug reactions should be distinguished from the physiological effects of the nerve block itself e.g. a decrease in blood pressure and bradycardia during spinal/epidural block.

Table 3 Table of adverse drug reactions

Within each system organ class, the ADRs have been ranked under the headings of frequency, most frequent reactions first.

Very common (>1/10)	<i>Vascular Disorders:</i> Hypotension ^a <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 ^b <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)

a Hypotension is less frequent in children (>1/100).
b Vomiting is more frequent in children. (>1/10).

*These symptoms usually occur because of inadvertent intravascular injection, overdose or rapid absorption, see section 4.9.

Class-related adverse drug reactions

Neurological complications

Neuropathy and spinal cord dysfunction (e.g. anterior spinal artery syndrome, arachnoiditis, cauda equina), which may result in rare cases of permanent sequelae, have been associated with regional anaesthesia, regardless of the local anaesthetic used.

Total spinal block

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

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 also section 4.4.

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

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. 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 even apnoea may occur. The respiratory and metabolic 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 system toxicity

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.

In children, early signs of local anaesthetic toxicity may be difficult to detect since they may not be able to verbally express them. *See also section 4.4.*

Treatment of acute systemic toxicity

See section 4.9 Overdose.

4.9 Overdose

Symptoms

Accidental intravascular injections of local anaesthetics may cause immediate (within seconds to a few minutes) systemic toxic reactions. 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. (*See section 4.8 Acute systemic toxicity, Central nervous system toxicity and Cardiovascular system toxicity*).

Treatment

If signs of acute systemic toxicity appear, injection of the local anaesthetic should be stopped immediately and CNS symptoms (convulsions, 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 occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, and or inotropic agents should be considered. Children should be given doses commensurate with age and weight.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, local, Amides

ATC code: N01B B09

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

The mechanism is a reversible reduction of the membrane permeability of the nerve fibre to sodium ions. Consequently the depolarisation velocity is decreased and the excitable threshold increased, resulting in a local blockade of nerve impulses.

The most characteristic property of ropivacaine is the long duration of action. Onset and duration of the local anaesthetic efficacy are dependant upon the administration site and dose, but are not influenced by the presence of a vasoconstrictor (e.g. adrenaline (epinephrine)). *For details concerning the onset and duration of action of Naropin, see Table 1 under posology and method of administration.*

Healthy volunteers exposed to intravenous infusions tolerated ropivacaine well at low doses and with expected CNS symptoms at the maximum tolerated dose. The clinical experience with this drug indicates a good margin of safety when adequately used in recommended doses.

5.2 Pharmacokinetic properties

Ropivacaine has a chiral center and is available as the pure S-(-)-enantiomer. It is highly lipid-soluble. All metabolites have a local anaesthetic effect but of considerably lower potency and shorter duration 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 $C_{\max}$ 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 in adults. 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.

Ropivacaine has a mean total plasma clearance in the order of 440 ml/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 -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 α_1 -acid glycoprotein. Variations in unbound, i.e. pharmacologically active, concentration have been much less than in total plasma concentration.

Since ropivacaine has an intermediate to low hepatic extraction ratio, its rate of elimination should depend on the unbound plasma concentration. A postoperative increase in AAG will decrease the unbound fraction due to increased protein binding, which will decrease the total clearance and result in an increase in total plasma concentrations, as seen in the paediatric and adult studies. The unbound clearance of ropivacaine remains unchanged as illustrated by the stable unbound concentrations during postoperative infusion. It is the unbound plasma concentration that is related to systemic pharmacodynamic effects and toxicity.

Ropivacaine readily crosses the placenta and equilibrium in regard to unbound concentration will be 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 than in the mother.

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% relates to unchanged drug. The major metabolite is 3-hydroxy-ropivacaine, about 37% of which is excreted in the urine, mainly conjugated. Urinary excretion of 4-hydroxy-ropivacaine, the N-dealkylated metabolite (PPX) and the 4-hydroxy-dealkylated accounts for 1-3%. Conjugated and unconjugated 3-hydroxy-ropivacaine shows only detectable concentrations in plasma.

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

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

Paediatrics

The pharmacokinetics of ropivacaine was characterized in a pooled population PK analysis on data in 192 children between 0 and 12 years. Unbound ropivacaine and PPX clearance and ropivacaine unbound volume of distribution depend on both body weight and age up to the maturity of liver function, 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. As PPX has a longer half-life and a lower clearance, it may accumulate during epidural infusion.

Unbound ropivacaine clearance (Cl_u) for ages above 6 months has reached values within the range of those in adults. Total ropivacaine clearance (CL) values displayed in Table 4 are those not affected by the postoperative increase in AAG.

Table 4 Estimates of pharmacokinetic parameters derived from the pooled paediatric population PK analysis

Age	BW ^a	Cl _u ^b	V _u ^c	CL ^d	t _{1/2} ^e	t _{1/2ppx} ^f
Group	kg	(L/h/kg)	(L/kg)	(L/h/kg)	(h)	(h)
Newborn	3.27	2.40	21.86	0.096	6.3	43.3
1m	4.29	3.60	25.94	0.143	5.0	25.7
6m	7.85	8.03	41.71	0.320	3.6	14.5
1y	10.15	11.32	52.60	0.451	3.2	13.6
4y	16.69	15.91	65.24	0.633	2.8	15.1
10y	32.19	13.94	65.57	0.555	3.3	17.8
a	Median bodyweight for respective age from WHO database.					
b	Unbound ropivacaine clearance					
c	Ropivacaine unbound volume of distribution					
d	Total ropivacaine clearance					
e	Ropivacaine terminal half life					
f	PPX terminal half life					

The simulated mean unbound maximal plasma concentration (Cu_{max}) after a single caudal block tended to be higher in neonates and the time to Cu_{max} (t_{max}) decreased with an increase in age (Table 4). Simulated mean unbound plasma concentrations at the end of a 72 h continuous epidural infusion at recommended dose rates also showed higher levels in neonates as compared to those in infants and children. See also section 4.4.

Table 5 Simulated mean and observed range of unbound Cumax after a single caudal block

Age group	Dose	Cu _{max} ^a	t _{max} ^b	Cu _{max} ^c
	(mg/kg)	(mg/L)	(h)	(mg/L)
0-1m	2.00	0.0582	2.00	0.05 – 0.08 (n=5)
1-6m	2.00	0.0375	1.50	0.02 – 0.09 (n=18)

6-12m	2.00	0.0283	1.00	0.01 – 0.05 (n=9)
1-10y	2.00	0.0221	0.50	0.01 – 0.05 (n=60)
a	Unbound maximal plasma concentration			
b	Time to unbound maximal plasma concentration			
c	Observed and dose-normalised unbound maximal plasma concentration			

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 systemic toxicity. Corresponding factors for the continuous epidural infusion are 1.8 and 3.8 respectively.

5.3 Preclinical safety data

Based on conventional studies of safety pharmacology, single and repeated dose toxicity, reproduction toxicity, mutagenic potential and local toxicity, no hazards for humans were identified other than those which can be expected on the basis of the pharmacodynamic action of high doses of ropivacaine (e.g. CNS signs, including convulsions, and cardiotoxicity).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid
Sodium hydroxide
Water for injections

6.2 Incompatibilities

Compatibilities with other solutions than those mentioned *in section 6.6* have not been investigated. In alkaline solutions precipitation may occur as ropivacaine shows poor solubility at pH > 6.0.

6.3 Shelf Life

2 years.

Shelf life after first opening:
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C.

For mixtures, see section 6.6.

6.4 Special precautions for storage

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

For storage after opening, see section 6.3

6.5 Nature and contents of container

100 ml polypropylene bags (Polybag®) in sterile blister packs of 5;
200 ml polypropylene bags (Polybag®) in sterile blister packs of 5.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Naropin® products are preservative free and are intended for single use only. Discard any unused solution.

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

Naropin solution for infusion in plastic infusion bags (Polybag) is chemically and physically compatible with the following drugs:

Concentration of Naropin: 1-2 mg/ml	
Additive	Concentration *
Fentanyl citrate	1.0 - 10.0 microgram/ml
Sufentanil citrate	0.4 - 4.0 microgram/ml
Morphine sulphate	20.0 - 100.0 microgram/ml
Clonidine hydrochloride	5.0 - 50.0 microgram/ml

* The concentration ranges stated in the table are wider than those used in clinical practice. Epidural infusions of Naropin/sufentanil citrate, Naropin/morphine sulphate and Naropin/clonidine hydrochloride have not been evaluated in clinical studies.

The mixtures are chemically and physically stable for 30 days at 20 to 30°C. From a microbiological point of view, the mixtures should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Ltd.,
600 Capability Green,
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UK

8 MARKETING AUTHORISATION NUMBER

PA 0970/047/001

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10 DATE OF REVISION OF THE TEXT

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