NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Naropin 2mg/mL Solution for Injection
Naropin 7.5mg/mL Solution for Injection
Naropin 10mg/mL Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for injection contains 2mg, 7.5mg or 10mg of ropivacaine hydrochloride.
For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

NAROPIN solution for injection is a sterile, isotonic, isobaric, aqueous solution.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NAROPIN is indicated for:

Surgical Anaesthesia

- Epidural block for surgery, including Caesarean Section
- Intrathecal block
- Major nerve block
- Field block (minor nerve block and infiltration)

Acute Pain Management

- Continuous epidural infusion (Naropin alone or in combination with Fentanyl) or intermittent bolus administration e.g. postoperative or labour pain
- Field block (minor nerve block and infiltration)
- Intra-articular injection
- Continuous peripheral nerve block infusion or intermittent injections, e.g. postoperative pain management
- Continuous wound infusion for postoperative pain management (adults only)

Acute Pain Management in Paediatrics (Children aged 0 – 12 years)

- Caudal epidural block in neonates, infants and children up to and including 12 years
- Peripheral nerve block in children aged 1 up to and including 12 years
- Continuous epidural infusion in neonates, infants and children up to and including 12 years

For peri- and postoperative pain management.

4.2 Dose and method of administration

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

ADULTS AND CHILDREN ABOVE 12 YEARS OF AGE:

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

In general, surgical anaesthesia (e.g. epidural administration) requires the use of the higher concentrations and doses. For analgesia the 2 mg/mL concentration of NAROPIN is generally recommended, except for intra-articular injection where the 7.5 mg/mL concentration is recommended.

Dosage Recommendations for NAROPIN in Adults

	Conc (mg/mL)	Volume (mL)	Dose (mg)
SURGICAL ANAESTHESIA			
Lumbar Epidural Administration			
Abdominal, pelvic and lower limb surgery	7.5	15-25	113-188
	10.0	15-20	150-200
Caesarean Section	7.5	15-20	113-150
Thoracic Epidural Administration			
To establish block for post-operative pain relief	7.5	5-15	38-113
Major Nerve Block			
(e.g. brachial plexus)	7.5	10-40	75-300 [1)]
Intrathecal Administration			
Surgery	5.0	3-4	15-20
Field Block			
(incl. minor nerve blocks and infiltration)	7.5	1-30	7.5-225
ACUTE PAIN MANAGEMENT			
Lumbar Epidural Administration			
Bolus (incl. labour pain management)	2.0	10-20	20-40
Intermittent Injection (top-up) (e.g. labour pain management)	2.0	10-15 (minimum interval 30 minutes)	20-30
Continuous infusion e.g.			
labour pain -	2.0	6-10 mL/h	12-20 mg/h
post operative pain management	2.0	6-14mL/h	12-28mg/h
Thoracic Epidural Administration			
Continuous infusion (eg, postoperative pain management)	2.0	6-14 mL/h	12-28 mg/h
In combination with Fentanyl for Epidural infusion			
Fentanyl 2 µg/mL	2.0	6-14 mL/h	12-28 mg/h *12-28 µg/h*
Fentanyl 4 µg/mL	2.0	6-14 mL/h	12-28 mg/h *24-56 µg/h*
Field Block			
(incl. minor nerve blocks and infiltration)	2.0	1-100	2-200
Intra-Articular Injection			
(e.g. single injection following knee arthroscopy)[3)]	7.5	20	150 [2)]

Peripheral Nerve Block			
(Femoral or interscalene block) Continuous infusion or intermittent injections (e.g. postoperative pain management)	2.0	5-10	10-20
Wound Infusion (adults only)			
Continuous infusion via surgical wound catheter for postoperative pain management[4]	2.0	4 – 10 mL/h	8-20 mg/h[5]

The doses in the table are those considered to be necessary to produce a successful block and should be regarded as guidelines for use in adults. Individual variations in onset and duration occur. The figures reflect the expected average dose range needed. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

1) The dose for a major nerve block must be adjusted according to site of administration and patient status. Interscalene and supraclavicular brachial plexus blocks may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used (See also Section 4.4).
2) If additional ropivacaine is used by any other techniques in the same patient an overall dose limit of 225mg should not be exceeded.
3) There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics. Naropin is not approved for this indication (See also Section 4.4).
4) A preinfusion loading bolus dose, sufficient to fill the wound catheter and wound space is recommended. Preinfusion wound tissue infiltration should also be considered.
5) Use for up to 48 hours only.

In order to avoid intravascular injection, aspiration should be repeated prior to and during administration of the main dose, which should be injected slowly or in incremental doses, at a rate of 25-50 mg/min, while closely observing the patient's vital functions and maintaining verbal contact. When an epidural dose is to be injected, a preceding test dose of 3-5 mL lignocaine (Xylocaine 1-2%) with adrenaline 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. If toxic symptoms occur, the injection should be stopped immediately.

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

When prolonged epidural blocks are used, either through continuous infusion or through repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. Cumulative doses up to 800 mg ropivacaine for surgery and post operative analgesia administered over 24 hours were well tolerated in adults, as were postoperative continuous epidural infusions at rates up to 28 mg/hour for 72 hours.

For treatment of postoperative pain, the following technique can be recommended: Unless preoperatively instituted, an epidural block with NAROPIN 7.5 mg/mL is induced via an epidural catheter. Analgesia is maintained with NAROPIN 2 mg/mL infusion. Clinical studies have demonstrated that infusion rates of 6-14 mL (12-28 mg), per hour provide adequate analgesia, with only slight and non-progressive motor block in most cases of moderate to severe postoperative pain. With this technique a significant reductions in the need for opioids have been observed.

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

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

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.

PAEDIATRICS

Dosage recommendations for 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 post operative)			
Caudal Epidural Administration (0 – 12 years) Blocks below T12, in children with a body weight up to 25 kg.	2.0	1	2
Peripheral Nerve Block (1 – 12 years*) (e.g. ilioinguinal nerve block)	5.0	0.6	3
Continuous Epidural Infusion (0 – 12 years) In children with body weight up to 25 kg			
0 up to 6 months			
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
6 to 12 months			
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
*1 to 12 years**			
Bolus dose[b]	2.0	1	2
Infusion up to 72 hours	2.0	0.2 mL/kg/h	0.4 mg/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.

* Including children 12 years of age

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 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. In children above 4 years of age, doses up to 3 mg/kg have been used safely. The volume of the caudal epidural injection may be adjusted to achieve a different distribution of sensory block, as recommended in standard textbooks.

For ilioinguinal block, a single injection of ropivacaine 5 mg /mL produces effective analgesia when a dose of 3 mg/kg in a volume of 0.6 mL/kg is used.

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

Concentrations above 5 mg/mL have not been documented for children.

Intrathecal administration has not been documented for use in children.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Regional anaesthetic procedures should always be performed in a properly equipped and staffed area. Equipment and medicines necessary for monitoring and emergency resuscitation should be immediately available. Patients receiving major blocks should be in an optimal condition and have an IV line inserted before the blocking procedure. The clinician responsible should take the necessary precautions to avoid intravascular injection (see Section 4.2) and be appropriately trained and familiar with diagnosis and treatment of side effects, systemic toxicity and other complications. (See SECTION 4.9).

Major peripheral nerve blocks may imply 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, which can lead to high plasma concentrations.

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

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

There have been rare reports of cardiac arrest during the use of NAROPIN for epidural anaesthesia of 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.

NAROPIN is metabolised in the liver and should therefore be used with caution in patients with severe liver disease and repeated doses may need to be reduced due to delayed elimination. Normally there is no need to modify the dose in patients with impaired renal function when used for single dose or short term treatment. Acidosis and reduced plasma protein concentration, frequently seen in patients with chronic renal failure may increase the risk of systemic toxicity (see Section 4.2).

Epidural and intrathecal anaesthesia may lead to hypotension and bradycardia. The risk of such effects can be reduced, e.g. by preloading the circulation or by injecting a vasopressor. Hypotension should be treated promptly with, for example, ephedrine 5-10 mg intravenously, repeated as necessary. Children should be given adrenaline doses commensurate with their age and weight.

Neonates need special attention due to immaturity of some organs and functions. This is especially important during continuous epidural infusion.

When Naropin® is administered as intra-articular injection, caution is advised when recent major intra-articular trauma is suspected or extensive raw surfaces within the joint have been created by the surgical procedure, as that may accelerate absorption and result in higher plasma concentrations.

Prolonged administration of ropivacaine should be avoided in patients treated with strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin (see Section 4.5).

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.

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

4.5 Interaction with other medicines 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 lignocaine and mexiletine, since the systemic toxic effects are additive. Specific interactions studies with ropivacaine and anti-arrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution is advised (see Section 4.4).

In healthy volunteers ropivacaine clearance was reduced by 77% during co-administration of fluvoxamine, a potent competitive inhibitor of P4501A2. CYP1A2 is involved in the formation of 3-hydroxy-ropivacaine, a major metabolite. Thus strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin, given concomitantly with Naropin can cause a metabolite interaction leading to an increased ropivacaine plasma concentration. Prolonged administration of ropivacaine should therefore be avoided in patients treated with strong inhibitors of CYP1A2 such as fluvoxamine and enoxacin (see Section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Apart from obstetrical use, there are no adequate data on the use of ropivacaine in pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see Section 5.3).

Intrathecal administration has not been documented for Caesarean section.

Lactation

The excretion of ropivacaine or its metabolites in human milk has not been studied. Based on the milk/plasma concentration ratio in rats, the estimated daily dose to a pup will be about 4% of the dose given to the mother. Assuming that the milk/plasma concentration ratio in humans is of the same order, the total ropivacaine dose to which the baby is exposed by breast feeding is far lower than by exposure *in utero* in pregnant women at term.

4.7 Effects on ability to drive and use machines

Besides the direct anaesthetic effect, local anaesthetics may have a very mild effect on mental function and 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 of other amide local anaesthetics. Adverse reactions caused by the drug *per se* are difficult to distinguish from the physiological effects of the nerve block (e.g. decrease in blood pressure, bradycardia), events caused directly (e.g.. nerve trauma) or indirectly (e.g. epidural abscess) by the needle puncture.

TABLE OF ADVERSE DRUG REACTIONS

(Pooled data from all types of blocks)

Very common (>1/10)	*Vascular Disorders*: Hypotension[c]
	Gastrointestinal Disorders: Nausea
Common (>1/100)	*Nervous system Disorders*: Paraesthesia, dizziness, headache[a]
	Cardiac Disorders: Bradycardia[a], tachycardia
	Vascular Disorders: Hypertension
	Gastrointestinal Disorders: Vomiting[a,d]
	Renal and Urinary Disorders: Urinary retention[a] *General Disorders and Administration Site Conditions*: Temperature elevation, rigor, back pain

Uncommon (>1/1,000)	*Psychiatric Disorders*: Anxiety
	Nervous System Disorders: Symptoms of CNS toxicity (convulsions, grand mal convulsions, seizures, light headedness, circumoral paraesthesia, numbness of the tongue, hyperacusis, tinnitus, visual disturbances, dysarthria, muscular twitching, tremor)[b], hypoaesthesia[a]
	Vascular Disorders: Syncope*
	Respiratory, Thoracic and Mediastinal Disorders: Dyspnoea[a]
	General Disorders and Administration Site Conditions: Hypothermia[a]
Rare (>1/10,000)	*Cardiac Disorders*: Cardiac arrest, Cardiac arrhythmias
	General Disorders and Administration Site Conditions: Allergic reactions (anaphylactic reactions, angioneurotic oedema and urticaria)

a These reactions are more frequent after spinal anaesthesia.
b These symptoms usually occur because of inadvertent intravascular injection, overdose or rapid absorption (see Section 4.9).
c Hypotension is less frequent in children (>1/100)
d Vomiting is more frequent in children (>1/10)

CLASS-RELATED ADVERSE DRUG REACTIONS

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

Neurological complications

Neuropathy and spinal cord dysfunctions (eg, anterior spinal artery syndrome, arachnoiditis, cauda equina), 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.

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 vascularised areas, (see 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 is a graded response with symptoms and signs of escalating severity. The first symptoms are usually light-headedness, circumoral paraesthesia, numbness of the tongue, hyperacusis, tinnitus and visual disturbances. Dysarthria, muscular twitching or tremors are more serious and precede the onset of generalised convulsions. These signs must not be mistaken for neurotic behaviour. Unconsciousness and grand mal convulsions may follow, which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly during convulsions due to the

increased muscular activity, together with the interference with respiration and possible loss of functional airways. In severe cases apnoea may occur. Acidosis, hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

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

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

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

Treatment of Acute Toxicity

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

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

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

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

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Accidental intravascular injections of local anaesthetics may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, systemic toxicity appears later (15-60 minutes after injection) due to the slower increase in local anaesthetic blood concentration (see Section 4.8).

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

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

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

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

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

Indirect cardiovascular effects (hypotension, bradycardia) may occur after epidural administration, depending on the extent of the concomitant sympathetic block, but is less commonly seen in children.

5.2 Pharmacokinetic properties

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

The plasma concentration of ropivacaine depends upon the dose, the route of administration and the vascularity of the injection site. Ropivacaine follows linear pharmacokinetics and the maximum plasma concentration is proportional to the dose.

Ropivacaine shows complete and biphasic absorption from the epidural space, with half-lives of the two phases of the order of 14 min and 4 h. The slow absorption is the rate-limiting factor in the elimination of ropivacaine, which explains why the apparent elimination half-life is longer after epidural than after intravenous administration. Ropivacaine 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, an unbound plasma clearance of 8 L/min, a renal clearance of 1 mL/min, a volume of distribution at steady state of 47 litres and a terminal half-life of 1.8 h after IV administration. Ropivacaine

has an intermediate hepatic extraction ratio of about 0.4. It is mainly bound to α_1-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.

Ropivacaine readily crosses the placenta and equilibrium with 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.

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

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

Impaired renal function has little or no influence on ropivacaine pharmacokinetics. The renal clearance of PPX is significantly correlated with creatinine clearance. A lack of correlation between total exposure, expressed as AUC, with creatinine clearance indicates that the total clearance of PPX includes a non-renal elimination in addition to renal excretion. Some patients with impaired renal function may show an increased exposure to PPX resulting from a low non-renal clearance. Due to the reduced CNS toxicity of PPX as compared to ropivacaine the clinical consequences are considered negligible in short-term treatment.

A similar pattern of major 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 characterised in a pooled population PK analysis of data in 192 children between 0 and 12 years from six studies . 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.

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 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 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 systemic toxicity. Corresponding factors for the continuous epidural infusion at 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

The solubility of ropivacaine is limited at pH values above 6. This must be taken into consideration when addition of alkaline solutions e.g. carbonates, is considered since precipitation might occur at higher pH values.

6.3 Shelf life

Polypropylene ampoules 10 mL, 20 mL (Polyamp® Duofit®)

NAROPIN 2.0 mg/mL, 7.5 mg/mL, 10.0 mg/mL: 36 months

Polypropylene infusion bags 100 mL, 200 mL (Polybag®)

NAROPIN 2.0 mg/mL: 24 months

6.4 Special precautions for storage

Store at or below 30°C. Avoid freezing.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Polyamp® Duofit®

NAROPIN 0.2% (2 mg/mL)
20 mL in Sterile AstraZeneca Theatre Pack™ (5's)

NAROPIN 0.75% (7.5 mg/mL)
10 mL and 20 mL in Sterile AstraZeneca Theatre Pack™ (5's)

NAROPIN 1% (10 mg/mL)
10 mL in Sterile AstraZeneca Theatre Pack™ (5's)

The ampoules are designed to fit Luer lock and Luer fit syringes

Polybag®

NAROPIN 0.2% (2 mg/mL)
100 mL and 200 mL in Sterile AstraZeneca Theatre Pack™ (5's)

6.6 Special precautions for disposal <and other handling>

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

The intact container must not be re-autoclaved. A blistered container should be chosen when a sterile exterior 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 mixtures are chemically and physically stable for 30 days at up 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.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pharmacy Retailing (NZ) Limited
Trading as Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
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9. DATE OF FIRST APPROVAL

6 June 1996

10. DATE OF REVISION OF THE TEXT

27 July 2017

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
	Update to the SPC-style format