

# NEW ZEALAND DATA SHEET

## 1 ROPIVACAINE-AFT

Ropivacaine 2mg/ml solution for injection or infusion.

Ropivacaine 7.5mg/ml solution for injection or infusion.

Ropivacaine 10mg/ml solution for injection or infusion.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of the solution contains 2mg, 7.5mg or 10mg of Ropivacaine hydrochloride

For full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection or infusion.

Ropivacaine base is a white to almost white powder which is practically insoluble in water, sparingly soluble in acetone and isopropyl alcohol and freely soluble in methanol.

ROPIVACAINE-AFT Solution for Injection is a clear, colourless, sterile, isotonic solution in which the Ropivacaine base has been converted to Ropivacaine hydrochloride.

The solution contains Ropivacaine hydrochloride in either 2.0 mg/mL, 7.5 mg/mL or 10.0 mg/mL concentrations. The pH of the solution is 4.5 –6.0.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ROPIVACAINE-AFT is indicated for

#### **Surgical anaesthesia in adults and children over 12 years of age:**

- Epidural block for surgery including caesarean section
- Intrathecal anaesthesia
- Field block (minor nerve block and infiltration)

#### **Major nerve block acute pain management**

- Continuous epidural infusion (Ropivacaine-AFT 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

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For per- and postoperative pain management

### 4.2 Dose and method of administration

Ropivacaine-AFT should only be administered by or under the supervision of clinicians experienced in regional anaesthesia.

Ropivacaine-AFT does not contain any anti-microbial agent. It should be used for one patient on one occasion only. Any unused product should be discarded.

The smallest dose required to produce effective anaesthesia should be administered and should be based upon the anaesthetic procedure, the area to be anaesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anaesthesia and degree of muscle relaxation required, the duration of anaesthesia desired, individual tolerance, and the physical condition of the patient. Patients in poor general condition due to aging or other compromising factors such as partial or complete heart conduction block, advanced liver disease or severe renal dysfunction require special attention although regional anaesthesia is frequently indicated in these patients. To reduce the risk of potentially serious adverse reactions, attempts should be made to optimize the patient's condition before major blocks are performed, and the dosage should be adjusted accordingly.

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

**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 containing 5 µg/mL adrenaline e.g. 3 mL lignocaine 2% with adrenaline 1:200,000 should be administered. Verbal contact and monitoring of heart rate and blood pressure should be maintained for 5 minutes after the test dose. If no signs of subarachnoid, intravascular or intrathecal injection, the main dose may be administered. A temporary increase in heart rate will result from an intravascular injection and a spinal block will indicate that intrathecal injection has occurred.

Prior to and during administration of the total dose, aspiration should be repeated.

Intrathecal injections should be administered after the subarachnoid space has been identified and clear CSF (cerebrospinal fluid) either seen to escape from the spinal needle or is detected by aspiration.

Ropivacaine-AFT solutions that are discoloured or contain particulate matter should not be administered.

The appropriate concentration and volume should be selected for the procedure. The 10 mg/mL concentration is recommended for epidural anaesthesia where profound motor block is required for surgery. No information is available on the use of concentrations higher than 7.5 mg/mL for caesarean section.

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## Dosage Recommendations for Adults

	Concentration mg/mL	Volume mL	Dose mg
<b>Surgical Anaesthesia</b>			
<b>Lumbar Epidural Administration</b>			
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
<b>Thoracic Epidural Administration</b> (to establish block for post-operative pain relief)	7.5	5-15	38-113
<b>Intrathecal Anaesthesia</b> surgery	5.0	3-4	15-20
<b>Major Nerve Block</b> e.g. brachial plexus	7.5	10-40	75-300 <sup>1</sup>
<b>Field Block</b> including minor nerve block and infiltration	7.5	1-40	5-200
<b>Acute Pain Management</b>			
<b>Lumbar Epidural Administration</b>			
Bolus including 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 post-operative pain management	2.0	6-10 mL/h	12-20 mg/h
	2.0	6-14 mL/h	12-28 mg/h
<b>Thoracic Epidural Administration</b>			
Continuous infusion e.g. post-operative pain	2.0	6-14 mL/h	12-28 mg/h
In combination with Fentanyl for Epidural infusion <i>Fentanyl 2 µg/mL</i>	2.0	6-14 mL/h	12-28 mg/h <i>12-28 µg/h</i>
	2.0	6-14 mL/h	12-28 mg/h <i>24-56 µg/h</i>
<b>Field Block</b> including minor nerve blocks and infiltration	2.0	1-100	2-200
<b>Intra-Articular Injection</b> e.g. single injection following knee arthroscopy <sup>3</sup>	7.5	20	150 <sup>2</sup>

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<b>Peripheral Nerve Block</b> (femoral or interscalene block) e.g. post-operative pain management	2.0	5-10	10-20
<b>Wound Infusion (adults only)</b> continuous infusion via surgical wound catheter for post-operative pain management <sup>4</sup>	2.0	4-10 mL/h	8-20 mg/h <sup>5</sup>

The doses in the table are those considered to be necessary to produce a successful anaesthesia 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. For other local anaesthetic techniques, standard current textbooks should be consulted.

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
2. If additional ropivacaine is used by any other techniques in the same patient an overall dose limit of 225 mg should not be exceeded.
3. There have been post-marketing reports of chondrolysis in patients receiving intra-articular continuous infusion of local anaesthetics. Ropivacaine-AFT is not approved for this indication.
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.

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. Experience to date indicates that a cumulative dose of up to 800 mg ropivacaine administered over 24 hours is well tolerated in adults. Caution should be exercised when administering ropivacaine for prolonged periods of time, especially in debilitated patients.

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

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 reduction in the need for opioids has been observed.

In clinical studies epidural infusion of ropivacaine 2 mg/mL alone or mixed with fentanyl 1-4 µg/mL has been given for postoperative pain management up to 72 hours. Ropivacaine 2 mg/mL (6-14 mL/hour) provided adequate pain relief for the majority of patients. The combination of ropivacaine 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 ropivacaine 7.5 mg/mL and interscalene block with 225 mg ropivacaine 7.5 mg/mL,

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respectively, before surgery. Analgesia was then maintained with ropivacaine 2 mg/mL. Infusion rates or intermittent injections of 10-20 mg per hour for 48 hours provided adequate analgesia and were well tolerated.

### Dosage Recommendations for paediatric patients up to and including 12 years of age

	Concentration mg/mL	Volume mL/kg	Dose mg/kg
<b>Acute Pain Management (Pre- and post-operative)</b>			
<b>Caudal Epidural Administration (0-12 years)</b> Blocks below T12 in children with a bodyweight up to 25 kg	2.0	1	2
<b>Peripheral Nerve Block (1-12 years)</b> e.g. ilioinguinal nerve block	5.0	0.6	3
<b>Continuous Epidural Infusion (0-12 years)</b> in children with a body weight up to 25 kg			
<i>0 up to 6 months</i>			
Bolus dose <sup>1</sup>			
Infusion up to 72 hours	2.0	0.5-1	1-2
	2.0	0.1 mL/kg/h	0.2 mg/kg/h
<i>6 to 12 months</i>			
Bolus dose			
Infusion up to 72 hours	2.0	0.5-1	1-2
	2.0	0.2 mL/kg/h	0.4 mg/kg/h
<i>1 to 12 years</i>			
Bolus dose <sup>2</sup>			
Infusion up to 72 hours	2.0	1	2
	2.0	0.2 mL/kg/h	0.4 mg/kg/h

1. 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.

2. 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.

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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**

Patients with a known allergy or hypersensitivity to ropivacaine or to any local anaesthetic agent of the amide type.

### **4.4 Special warnings and precautions for use**

#### General

The safe and effective use of local anaesthetics depends on correct dosage and technique, adequate precautions and readiness for emergencies. Resuscitative equipment, oxygen and resuscitative drugs e.g. vasopressor and vagolytic drugs should be available for immediate use. An I.V. cannula should be inserted before ropivacaine is administered due to the possibility of hypotension or bradycardia occurring after major blocks.

The lowest dosage that results in effective anaesthesia should be used. Injections should be made slowly and incrementally, with frequent aspirations to avoid intravascular injection. When a continuous catheter technique is used, syringe aspirations should also be performed before and during each supplemental injection. During the administration of epidural anaesthesia, it is recommended that a test dose of a local anaesthetic with a fast onset be administered initially and that the patient be monitored for central nervous system and cardiovascular toxicity, as well as for signs of unintended intrathecal, subarachnoid or intravascular administration before proceeding (see section 4.2).

Debilitated, elderly patients and acutely ill patients including those with complete heart conduction block, advanced liver disease or severe renal impairment should be given reduced doses commensurate with their age and physical condition

Careful and constant monitoring of cardiovascular and respiratory vital signs (adequacy of ventilation) and the patient's state of consciousness should be performed after each local anaesthetic injection. It should be kept in mind at such times, that restlessness, anxiety, incoherent speech, light-headedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.

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Because ropivacaine is metabolized by the liver, it should be used cautiously in patients with severe hepatic disease. Repeated doses may need to be reduced due to the increased elimination half-life.

When ropivacaine is used for a single dose or for short term treatment, dosage modification is not normally required for patients with impaired renal function. However, acidosis and reduced plasma protein concentration are often observed in patients with chronic renal dysfunction which may increase the risk of systemic toxicity.

Local anaesthetics should be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.

When epidural/spinal (neuraxial) anaesthesia is used, patients who have been or are to be treated with low molecular weight heparins or heparinoid anti-coagulants are at risk of developing epidural or spinal haemotoma which may cause long-term or permanent paralysis. This risk is increased by the use of in-dwelling epidural catheters, traumatic or repeated epidural/spinal puncture and concomitant use of other haemostatis effecting medication e.g. NSAIDS, platelet inhibitors, other anti-coagulants. Patients should be monitored for signs and symptoms of neurological impairment.

Hypotension and bradycardia may occur after epidural or intrathecal anaesthesia. The risk of these effects may be reduced by preloading the circulation or by injection a vasopressor. Hypotension should be treated promptly e.g. ephedrine 5-10 mg IV repeated as required.

Ropivacaine should be used with caution in patients with known drug sensitivities.

Local anaesthetics should only be used with extreme caution (if used at all) in patients with pre-existing abnormal neurological pathology e.g. myasthenia gravis, or as epidural, caudal or spinal anaesthesia in patients with serious diseases of the CNS or spinal cord e.g. meningitis, spinal fluid block, cranial or spinal haemorrhage, tumours, poliomyelitis, syphilis, tuberculosis or metastatic lesions of the spinal cord.

If ropivacaine is administered simultaneously by 2 or more routes the total dose and risk of systemic toxicity should be considered.

Patients treated with class III antiarrhythmic drugs (e.g. amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive.

Ropivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, since the toxic effects of these drugs are additive

There have been reports of cardiac arrest when ropivacaine has been used for epidural anaesthesia or peripheral nerve blockade, especially after inadvertent intravascular administration, in the elderly and patients with concomitant heart disease. Resuscitation has been difficult in some cases. Prolonged resuscitation may be required if cardiac arrest occurs.

Caution is advised when ropivacaine is administered by intra-articular injection and recent major intra-articular damage is suspected or raw surfaces within the joint have been created by the surgical procedure as the rate of absorption may be increased resulting in higher plasma concentrations.

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Prolonged use in patients being treated with strong CYP1A2 inhibitors e.g. fluvoxamine and enoxacin should be avoided.

Ropivacaine may be porphyrinogenic and should only be used in patients with acute porphyria when no safer alternative is available. Appropriate precautions should be taken.

### Use in Peripheral Nerve Block

Major peripheral nerve blocks may result in 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.

### Use in Head and Neck Area

Small doses of local anaesthetics injected into the head and neck area including retrobulbar, dental and stellate ganglion blocks may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care. Confusion, convulsions, respiratory depression, and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anaesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration constantly monitored.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals to evaluate the carcinogenic potential have not been conducted.

Ropivacaine hydrochloride was negative in the Ames salmonella/mammalian microsome mutagenicity, 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* with weak mutagenic activity seen in the mouse lymphoma test. Clinical use of ropivacaine is unlikely to pose a risk of genotoxicity.

Studies in rats did not demonstrate an effect on fertility or general reproductive performance when ropivacaine was administered over 2 generations.

### **4.5 Interaction with other medicines and other forms of interaction**

Safety data generated in clinical studies indicates that ropivacaine has a safety profile similar to other local anaesthetics of the amide type.

Trials studying the interaction between ropivacaine and class III antiarrhythmic drugs e.g. amiodarone have not been performed, but caution is advised (see section 4.4).

Ropivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics as the toxic effects of these drugs are additive.

Cytochrome P4501A2 is involved in the formation of 3-hydroxy ropivacaine, the major metabolite. In vivo, the plasma clearance of ropivacaine was reduced by 70% during co-administration of fluvoxamine, a selective and potent CYP1A2 inhibitor. Single doses of



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ropivacaine should be used with care in patients concomitantly receiving a potent CYP1A2 inhibitor while repeated administration or long term infusion should be avoided. Caution should be exercised when potent CYP1A2 inhibitors are co-administered.

Co-administration of a selective and potent inhibitor of CYP3A4, (ketoconazole) caused a 15% reduction in in-vivo plasma clearance of ropivacaine.

Cimetidine, a CYP2E1 inhibitor, inhibited the formation of minor metabolites in vitro but did not inhibit the formation of 3-hydroxy-ropivacaine.

The solubility of ropivacaine decreases at pH levels above 6.0. This should be considered if adding an alkaline solution as precipitation may occur.

A reduction in liver blood flow is not expected to have a significant effect on ropivacaine clearance.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

Category B1

Reproduction toxicity studies have been performed in pregnant New Zealand white rabbits and Sprague-Dawley rats. During gestation days 6-18, rabbits received 1.3, 4.2, or 13 mg/kg/day subcutaneously. In rats, subcutaneous doses of 5.3, 11 and 26 mg/kg/day were administered during gestation days 6-15. No teratogenic effects were observed. The highest doses of 13 mg/kg/day (rabbits) and 26 mg/kg/day (rats) are approximately 1/3 of the maximum recommended human dose (epidural, 770 mg/24 hours) based on a mg/m<sup>2</sup> basis. In prenatal and postnatal studies, the female rats were dosed daily from day 15 of gestation to day 20 postpartum. The doses were 5.3, 11 and 26 mg/kg/day subcutaneously. There were no treatment-related effects on late foetal development, parturition, lactation, neonatal viability, or growth of the offspring. In a further study with rats, the males were dosed daily for 9 weeks before mating and during mating. The females were dosed daily for 2 weeks before mating and then during the mating, pregnancy, and lactation, up to day 42 post coitus. At 23 mg/kg/day, an increased loss of pups was observed during the first 3 days postpartum. The effect was considered secondary to impaired maternal care due to maternal toxicity.

There are no adequate or well-controlled studies in pregnant women of the effects of ropivacaine on the developing foetus. Ropivacaine should only be used during pregnancy if the benefits outweigh the risk.

#### Labour and Delivery

Local anaesthetics, including ropivacaine, rapidly cross the placenta, and when used for epidural block can cause varying degrees of maternal, foetal and neonatal toxicity. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, foetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

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Maternal hypotension has resulted from regional anaesthesia with ropivacaine. Local anaesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The foetal heart rate also should be monitored continuously, and electronic foetal monitoring is highly advisable. Epidural anaesthesia has been reported to prolong the second stage of labour by removing the patient's reflex urge to bear down or by interfering with motor function. Spontaneous vertex delivery occurred more frequently in patients receiving ropivacaine than in those receiving bupivacaine.

### Nursing Mothers

Some local anaesthetic drugs are excreted in human milk and caution should be exercised when they are administered to a nursing woman. 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 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.

### **4.7 Effects on ability to drive and use machines**

No data are 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**

Reactions to ropivacaine are characteristic of those associated with other amide-type local anaesthetics. A major cause of adverse reactions to this group of drugs may be associated with excessive plasma levels, which may be due to overdosage, rapid absorption, unintentional intravascular injection or slow metabolic degradation. They may be difficult to distinguish from the physiological effects of the nerve block or events caused by needle puncture.

Acidosis, hyperkalaemia or hypoxia in patients may increase the likelihood and severity of toxic reactions.

Systemic overdose or intravascular injection may affect the CNS and/or the cardiovascular system. Subarachnoid injection may result in depression of the CNS, respiratory arrest and cardiovascular arrest.

#### **Incidence > 10%**

Hypotension and Nausea

#### **Incidence > 1%**

Urinary retention, back pain, chest pain, pain, oliguria, insomnia, dizziness, rigors, headache, temperature elevation, paraesthesia, bradycardia, hypertension, tachycardia and vomiting

#### **Incidence ≤ 1%**

Serious but less common reactions reflecting systemic toxicity include dysarthria, muscular rigidity, muscle twitching, unconsciousness, convulsions, hypoxia, hypercapnia, apnoea,

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severe hypotension, arrhythmias and cardiac arrest. Convulsions, grand mal convulsions and seizures have been observed.

Other adverse effects noted include anxiety, hypoaesthesia, syncope, dyspnoea, hypothermia, **Incidence  $\leq$  0.1%**

Cardiac arrest, cardiac arrhythmias, allergic reactions including anaphylactoid reactions, angioneurotic oedema and urticaria.

### **Class-related Adverse Effects**

These complications relate to anaesthetic technique regardless of the local anaesthetic used:

- Neuropathy and spinal cord dysfunctions e.g. anterior spinal artery syndrome, arachnoiditis, cauda equina syndrome have been associated with intrathecal and epidural anaesthesia
- Total spinal block may occur if an epidural dose is given intrathecally or if an intrathecal dose is too large
- Systemic toxic reactions primarily involve the central nervous and cardiovascular systems. They are caused by high blood concentration of the local anaesthetic which may be caused by intravascular injection, overdose or rapid absorption. For further information refer to section 4.9.

### **Foetal, Neonatal and Infant Adverse Effects**

These effects have been observed in the baby in-utero and peri- or post-partum when ropivacaine was administered to pregnant women:

- Incidence  $>$  1%: Foetal distress, tachycardia and bradycardia, neonatal vomiting, respiratory disorders, tachypnoea, fever and jaundice
- Incidence  $<$  1%: Foetal acidosis, neonatal hypoglycaemia and vomiting, hypotonia and low Apgar score.

### **Reporting of suspected adverse reactions**

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**

Acute emergencies from local anaesthetics are generally related to high plasma levels or to unintended subarachnoid or intravascular injection of the local anaesthetic solution (see section 4.8).

If overdose occurs. Peak plasma levels may not be reached for 1-2 hours depending upon the injection site thus signs of toxicity may be delayed. Systemic toxic reactions may involve the CNS and cardiovascular systems. Early signs of toxicity may be difficult to detect where the block is given during deep sedation or general anaesthesia.

Due to the low dose administered, systemic toxicity after intrathecal administration is expected to be low. However an excessive dose given into the intrathecal space may cause total spinal block.

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### Symptoms

CNS toxicity is a graded response with symptoms of increasing severity. Initial symptoms include visual or audio disturbances, peri-oral numbness, dizziness, light-headedness, tingling and paraesthesia. Dysarthria and muscular rigidity and twitching are more serious and may precede generalised convulsions. Unconsciousness and grand mal convulsions (may last from a few seconds to several minutes) may follow. Hypoxia and hypercapnia occur rapidly during convulsions due to increased muscle activity, respiration disruption and possible loss of functional airways. In severe cases apnoea may occur. Respiratory and metabolic acidosis, hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

Recovery follows redistribution of the drug from the CNS followed by metabolism and excretion. Recovery is normally rapid.

Cardiovascular toxicity is a more serious event. Hypotension, bradycardia, arrhythmia and cardiac arrest may occur. Cardiovascular toxic effects are usually preceded by signs of CNS toxicity unless the patient is receiving a general anaesthetic or is heavily sedated with benzodiazepines, barbiturates or similar. In rare cases cardiac arrest has occurred without prodromal CNS effects.

### Treatment

Therapy with ropivacaine should be discontinued at the first sign of toxicity. Treatment should be symptomatic and supportive ensuring adequate ventilation and stopping of convulsions. If required assisted or controlled ventilation should be maintained with oxygen.

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

If cardiovascular depression is observed e.g. hypotension, bradycardia treatment with intravenous fluids, vasopressor or inotropic agents may be required.

Pulmonary resuscitation should be started and maintained if ventricular fibrillation or cardiac or circulatory arrest occur. Should cardiac arrest occur, prolonged resuscitative efforts may be required to improve the probability of a successful outcome.

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

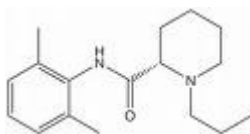
## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Ropivacaine has the chemical name (-)-1-propyl-2',6'-pipercoloxylidide. It has the molecular formula C<sub>17</sub>H<sub>26</sub>N<sub>2</sub>O with a molecular weight of 274.4. The CAS number is 84057-95-4.

The structural formula is:

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Ropivacaine hydrochloride is a member of the amide class of local anaesthetics and is supplied as the S-(-)-enantiomer. At high doses it results in surgical anaesthesia while at lower doses it causes sensory block (analgesia) with limited motor block.

Local anaesthetics act by preventing the generation and transmission of impulses along nerve fibres and at nerve endings; depolarisation and ion exchange are inhibited. The effects are reversible. They are used for the local relief of painful conditions and to prevent pain and discomfort of various medical and surgical procedures. In general, loss of pain occurs before loss of sensory and autonomic function and loss of motor function but this is dependent upon the drug used and the site to which it is given.

Onset and duration of the local anaesthetic effect of ropivacaine is dependent upon the dose and site of administration. The presence of a vasoconstrictor such as adrenaline has little effect.

Studies of the local anaesthetic effect have been undertaken for ropivacaine which demonstrated that the S-(-) form is less toxic and/or has a longer duration of action than the R-(+) form. In vitro testing indicates that ropivacaine is comparable to (or slightly more potent than) bupivacaine in blocking sensory fibres and less active in blocking motor fibres.

Multiple animal studies for peripheral (sciatic nerve and brachial plexus) neural block indicates that ropivacaine concentrations of 0.5-1.0% produce effective sensory and motor block but that neither increasing the concentration above 0.75% nor adding adrenaline, significantly improved the duration of the motor block or the anaesthetic effect of ropivacaine.

Animal studies for central neural blockade indicated that onset times for epidural anaesthesia were similar for ropivacaine and bupivacaine. To produce complete motor blockade with epidural anaesthesia, concentrations of ropivacaine of 0.75-1.0% appear to be required. Duration of sensory block is comparable for equal concentrations of ropivacaine and bupivacaine.

Infiltration anaesthesia tests in guinea pigs indicated that ropivacaine is superior to bupivacaine in producing sustained anaesthesia. The duration of anaesthesia with the least effective ropivacaine concentration exceeded that produced by the highest bupivacaine concentration.

Studies in both animals and man indicate that ropivacaine is less toxic than bupivacaine with respect to the CNS and cardiovascular systems, but that for a given dose lignocaine is less toxic than ropivacaine.

In rat studies, ropivacaine interacted in a similar manner to bupivacaine and lignocaine with other agents used with local anaesthetics e.g. benzodiazepines, thiopental, enflurane, pancuronium, suxamethonium and fentanyl. Ropivacaine also potentiated the sedative effect of morphine.

### 5.2 Pharmacokinetic properties

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### **Absorption**

The systemic concentration of ropivacaine is dependent on the total dose and concentration of drug administered, the route of administration, the patient's hemodynamic/circulatory condition, and the vascularity of the administration site. From the epidural space, ropivacaine shows complete and biphasic absorption. The half-lives of the 2 phases are approximately 14 minutes and 4 hours respectively. The slow absorption is the rate limiting factor in the elimination of ropivacaine explaining why the terminal half-life is longer after epidural than after intravenous administration. Ropivacaine shows linear pharmacokinetics and the maximum plasma concentration is proportional to the dose

### **Distribution**

After I.V. administration, ropivacaine has a total plasma clearance of approximately 440 mL/min, an unbound plasma clearance of 8 L/min, renal clearance of 1 mL/min, a steady state volume of distribution of 47 litres and a terminal half-life of 1.8 hours. Ropivacaine is 94% protein bound, mainly to  $\alpha_1$ -acid glycoprotein. An increase in total plasma concentrations during continuous epidural and interscalene infusion has been observed, related to a postoperative increase of  $\alpha_1$ -acid glycoprotein. Variations in unbound, i.e. pharmacologically active, concentrations have been less than in total plasma concentration. Ropivacaine readily crosses the placenta and equilibrium in regard to unbound concentration will be rapidly reached. The degree of plasma protein binding is less in the foetus than the mother resulting in lower total plasma concentrations in the foetus than the mother.

### **Metabolism**

Ropivacaine is extensively metabolized in the liver, predominantly by aromatic hydroxylation mediated by cytochrome P4501A to 3-hydroxy ropivacaine and N-dealkylation to PPX (2,6-pipecoloxylidide) mediated by CYP3A4. After a single IV dose approximately 37% of the total dose is excreted in the urine as both free and conjugated 3-hydroxy ropivacaine. Low concentrations of 3-hydroxy ropivacaine have been found in the plasma. Urinary excretion of 4-hydroxy ropivacaine, PPX and 4-hydroxy-dealkylated metabolite accounts for less than 3% of the dose. An additional metabolite, 2-hydroxy-methyl-ropivacaine, has been identified but not quantified in the urine. PPX and 3-OH-ropivacaine are the major metabolites excreted in the urine during epidural infusion. Total PPX concentration in the plasma was about half that of total ropivacaine; however, mean unbound concentrations of PPX were about 7 to 9 times higher than that of unbound ropivacaine following continuous epidural infusion for up to 72 hours. Unbound PPX, 3-hydroxy and 4-hydroxy ropivacaine, have a pharmacological activity in animal models less than that of ropivacaine. There is no evidence of in vivo racemization in urine of ropivacaine.

### **Elimination**

The kidney is the main excretory organ for most local anaesthetic metabolites. In total, 86% of the ropivacaine dose is excreted in the urine after intravenous administration of which only 1% relates to unchanged drug.

#### Pharmacokinetics during pregnancy

In pregnancy at term, after epidural administration ropivacaine clearance is lower and its unbound clearance approximately half that observed in non-pregnant patients. Thus total  $C_{max}$

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and unbound  $C_{\max}$  are higher in pregnancy. Unbound plasma concentration in the umbilical cord at delivery were similar to those in the mother and showed relatively rapid equilibrium. There was no obvious correlation between neonatal neurological and adaptive capacity scores and the unbound or total plasma concentration in the newborn infants.

### Paediatric Use

The pharmacokinetics of ropivacaine when used in children was determined using studies involving 192 children aged between 0 – 12 years. Unbound ropivacaine, PPX clearance and the ropivacaine unbound volume of distribution are dependent upon both bodyweight and age until liver function maturity and subsequently on body weight alone. 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.

### Clinical Trials

Ropivacaine was studied as a local anaesthetic for surgical anaesthesia. The onset, depth and duration of sensory block are, in general, similar to bupivacaine. However, the depth and duration of motor block, in general, are less than that with bupivacaine.

### **Epidural Administration in Surgery**

In studies performed to evaluate ropivacaine epidural injection for general surgery, ropivacaine was used in doses ranging from 75 to 250 mg. In doses of 100-200 mg, the median onset time

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to achieve a T10 sensory block was 10 minutes and the median duration at the T10 level was 4 hours. Higher doses produced a more profound block with a greater duration of effect.

### **Epidural Administration in Caesarean Section**

Studies have been performed with epidural administration of ropivacaine for caesarean section. Eight of these studies involved 218 patients using the concentration of 5 mg/mL in doses up to 150 mg. Median onset measured at T6 ranged from 11-26 minutes. Median duration of sensory block at T6 ranged from 1.7-3.2 hours, and duration of motor block ranged from 1.4-2.9 hours. Ropivacaine provided adequate muscle relaxation for surgery in all cases.

Further studies for caesarean section were performed in 264 patients at a concentration of 7.5 mg/mL in doses up to 187.5 mg. Median onset measured at T6 ranged from 4-15 minutes. 77-96% of ropivacaine-exposed patients reported no pain at delivery. Some patients received other anaesthetic, analgesic, or sedative modalities during the course of the operative procedure.

### **Peripheral Nerve Block**

Ropivacaine, 5 mg/mL, was evaluated for its ability to provide anaesthesia for surgery using the techniques of Peripheral Nerve Block. Studies performed included a series of 4 pharmacodynamic and pharmacokinetic studies performed on minor nerve blocks. From these, 235 ropivacaine treated patients were evaluable for efficacy. Ropivacaine was used in doses up to 275 mg. When used for brachial plexus block, onset depended on technique used. Supraclavicular blocks were consistently more successful than axillary blocks. The median onset of sensory block (anaesthesia) produced by ropivacaine via axillary block ranged from 10 minutes (medial brachial cutaneous nerve) to 45 minutes (musculocutaneous nerve). Median duration ranged from 3.7 hours (medial brachial cutaneous nerve) to 8.7 hours (ulnar nerve). The 5 mg/mL ropivacaine solution gave success rates from 56% to 86% for axillary blocks, compared with 92% for supraclavicular blocks.

Ropivacaine, 7.5 mg/mL was evaluated in 99 ropivacaine treated patients, in 2 double-blind studies, performed to provide anaesthesia for surgery using the techniques of Brachial Plexus Block. Ropivacaine 7.5 mg/mL was compared to bupivacaine 5 mg/mL. In 1 study, patients underwent axillary brachial plexus block using injections of 40 mL of ropivacaine, 7.5 mg/mL or 40 mL injections of bupivacaine, 5 mg/mL. In the second study, patients underwent subclavian perivascular brachial plexus block using 30 mL of ropivacaine, 7.5 mg/mL or 30 mL of bupivacaine 5 mg/mL. There was no significant difference between the ropivacaine and bupivacaine groups in either study with respect to onset of anaesthesia, duration of sensory blockade, or duration of anaesthesia.

The median duration of anaesthesia varied between 11.4-14.4 hours with both techniques. In one study, using the axillary technique, the quality of analgesia and muscle relaxation in the ropivacaine group was judged to be significantly superior to bupivacaine by both investigator and surgeon. However, using the subclavian perivascular technique, no statistically significant difference was found in the quality of analgesia and muscle relaxation as judged by both the investigator and surgeon. The use of ropivacaine 7.5 mg/mL for block of the brachial plexus via either the subclavian perivascular approach using 30 mL (225 mg) or via the axillary approach using 40 mL (300 mg) both provided effective and reliable anaesthesia.



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### 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

Hydrochloric acid

Potassium hydroxide

Sodium chloride

Water for injection

### 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

24 months.

Shelf life after opening: 24 hours when stored at 2° to 8°C.

### 6.4 Special precautions for storage

Store at or below 30°C. Protect from light.

After opening: stored at 2° to 8°C (Refrigerate, do not freeze).

### 6.5 Nature and contents of container

Ropivacaine 2 mg/mL, solution for injection, 10 mL and 20 mL vials, packs of 5 vials

Ropivacaine 7.5 mg/mL, solution for injection, 10 mL and 20 mL vials, packs of 5 vials

Ropivacaine 10 mg/mL, solution for injection, 10 mL and 20 mL vials, packs of 5 vials

Ropivacaine 2 mg/mL, solution for infusion, 100 mL bag, packs of 1 and 10 bags

Ropivacaine 2 mg/mL, solution for infusion, 200 mL bag, packs of 1 and 5 bags

### 6.6 Special precautions for disposal and other handling

Ropivacaine is 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.

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Ropivacaine solution for infusion is chemically and physically compatible with the following drugs:

<b>Concentration of Ropivacaine: 1-2 mg/ml</b>	
<b>Additive</b>	<b>Concentration*</b>
Fentanyl citrate	1.0 - 10.0 microgram/ml
Sufentanil citrate	0.4 - 4.0 microgram/ml
Morphine sulfate	20.0 - 100 microgram/ml
Clonidine hydrochloride	5.0 - 50 microgram/ml

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

The medicinal product should be visually inspected prior to use. The solution should only be used if it is clear, practically free from particles and if the container is undamaged.

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 to 8°C.

### 7 MEDICINE SCHEDULE

Prescription only medicine

### 8 SPONSOR

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### 9 DATE OF FIRST APPROVAL

2/12/2010

### 10 DATE OF REVISION OF THE TEXT

March 2019

### SUMMARY TABLE OF CHANGES

<b>Date</b>	<b>Section(s) Changed</b>	<b>Change (s)</b>
March 2019	All	Reformat consistent with new Medsafe Data Sheet Template.