NEW ZEALAND DATA SHEET

1. ROPIVACAINE-AFT 2 mg/mL SOLUTION FOR INFUSION

Ropivacaine hydrochloride 2 mg/mL (0.2%) solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of Ropivacaine-AFT solution for infusion contains 2 mg ropivacaine hydrochloride.

For the full list of excipients, see **Section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Solution for infusion.

Ropivacaine-AFT solution for infusion is a clear, colourless, sterile, isotonic, isobaric, aqueous solution and is practically free from visible particles.

The solution has a pH of 4.0 – 6.0 and an osmolality of 270 – 340 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Ropivacaine-AFT is indicated for:

<u>Surgical analgesia</u>

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

<u>Acute pain management</u>

- Continuous epidural infusion (Ropivacaine-AFT alone or in combination with fentanyl) or intermittent bolus epidural administration for analgesia in post-operative pain or labour pain
- Field block (minor nerve block and infiltration)
- Intra-articular injection
- Continuous peripheral nerve block infusion or intermittent injections e.g. for post-operative pain management

- Continuous wound infusion for post-operative 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 post-operative pain management.
There are no safety or efficacy data to support the use of Ropivacaine-AFT for analgesia for longer than 72 hours. (Data for peripheral nerve block administered as a continuous peripheral infusion or intermittent injections and for continuous wound infusion support the use for up to 48 hours only).

4.2. Dose and method of administration

Ropivacaine-AFT should only be used by or under the supervision of clinicians experienced in analgesia.

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 Ropivacaine-AFT is generally recommended, except for intra-articular injection where the 7.5 mg/mL concentration is recommended.

Table 1: Recommended dosages for Ropivacaine-AFT solution in the average, healthy, 70 kg adult patient.

	Conc. (mg/mL)	Volume (mL)	Dose* (mg)
SURGICAL ANALGESIA			
Lumbar epidural administration			
Abdominal, pelvis and lower limb surgery	7.5 10.0	15 – 25 15 – 20	113 – 188 150 – 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

	Conc. (mg/mL)	Volume (mL)	Dose* (mg)
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 – 14 mL/h	12 – 28 mg/h
Thoracic epidural administration			
Continuous infusion e.g. post-operative pain management	2.0	6 – 14 mL/h	12 – 28 mg/h
In combination with fentanyl for epidural infurion			
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. post-operative pain management)	2.0	5 – 10	10 – 20

Wound infusion (adults only) Continuous infusion via surgical wound catheter for post-operative 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 product 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 Special warnings and precautions for use**).

(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 post-operative intra-articular continuous infusion of local anaesthetics. Ropivacaine hydrochloride solution for injection is not approved for this indication (See also **Section 4.4 Special warnings and precautions for use**).

(4) A pre-infusion loading bolus dose, sufficient to fill the wound catheter and wound space is recommended. Pre-infusion wound tissue infiltration should also be considered.

(5) Use for up to 48 hours only.

NOTE

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 lignocaine (Xylocaine 1 – 2%) with adrenaline should be used. Note the presence of any symptoms or signs which are indicative of unintentional intravascular injection (temporary increased heart rate) or unintentional intrathecal injection (spinal block). If toxic symptoms occur, stop the injection immediately.

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

Analgesia

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 by 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 of up to 800 mg ropivacaine for surgery and post-operative analgesia administered over 24 hours were well tolerated in adults, as were post-operative continuous epidural infusions at rates

up to 28 mg/hour for 72 hours.

When calculating the dosage for post-operative analgesia, the use of intraoperative local anaesthetic/s should be taken into account.

For treatment of post-operative pain, the following technique can be recommended: Unless preoperatively instituted, an epidural block with ropivacaine hydrochloride 7.5 mg/mL solution for injection is induced via an epidural catheter. Once epidural block is achieved, epidural analgesia is maintained with Ropivacaine-AFT 2 mg/mL solution for infusion. Clinical studies have demonstrated that infusion rates of 6 – 14 mL/h (12 – 28 mg/h) provide adequate analgesia, with only slight and non-progressive motor block in most cases of moderate to severe post-operative pain. With this technique a significant reduction in the need for opioids has been observed.

In clinical studies epidural infusion of ropivacaine hydrochloride 2 mg/mL solution for infusion alone or mixed with fentanyl 1 – 4 µg/mL has been given for post-operative pain management up to 72 hours. Data for peripheral nerve block administered as a continuous peripheral infusion or intermittent injections support the use for up to 48 hours only at dosages of 10 – 20 mg/h (5 – 10 mL/h). The combination of ropivacaine hydrochloride 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 risk of reaching a toxic plasma concentration or inducing local neural injury must be considered.

In clinical studies, femoral nerve block was established with 300 mg ropivacaine hydrochloride 7.5 mg/mL solution for injection and interscalene block with 225 mg ropivacaine hydrochloride 7.5 mg/mL solution for injection, respectively, before surgery. Analgesia was then maintained with ropivacaine hydrochloride 2 mg/mL solution for infusion. Infusion rates or intermittent injections of 10 – 20 mg/h for 48 hours provided adequate analgesia and were well tolerated.

Use in children (aged 0 – 12 years)

Table 2: 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 (Pre- and post-operative)			

	Conc. (mg/mL)	Volume (mL/kg)	Dose (mg/kg)
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 (31 days – 12 years*) In children with body weight 2.5 kg to 25 kg			
31 days 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 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 hydrochloride 0.2% (2 mg/mL) produces adequate post-operative analgesia below T12 in the majority of patients when a dose of 2 mg/kg is used in a volume of 1 mL/kg. In children above 4 years of age, doses up to 3 mg/kg have been used safely by the caudal route. The volume of the caudal epidural injection may be adjusted to achieve a different distribution to 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 hydrochloride 2 mg/mL solution for infusion in premature children has not been documented.

Use in debilitated or elderly patients
Debilitated or elderly patients, including those with partial or complete heart conduction block, advanced liver disease or severe renal dysfunction should be given reduced dosage commensurate with their physical condition. Clinical studies with this group of patients have not been performed (see **Section 4.4 Special warnings and precautions for use**).

4.3. Contraindications

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

4.4. Special warnings and precautions for use

Accuracy of dose and technique
The safety and efficacy of Ropivacaine-AFT depends on proper dosage, correct technique and adequate precautions. Standard textbooks should be consulted regarding specific techniques and precautions for various regional anaesthetic procedures.

The lowest dosage that results in efficacious anaesthesia should be used (see **Section 4.2 Dose and method of administration**).

If ropivacaine hydrochloride is administered simultaneously by two or more different routes, the total dose and hence the risk of systemic toxicity should be considered.

Emergency resuscitation
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 Dose and method of administration, Adults and children above 12 years of age**) and be appropriately trained and familiar with diagnosis and treatment of side effects, systemic toxicity and other complications (see **Section 4.9 Overdose**).

Peripheral nerve block
Major peripheral nerve blocks may involve the administration of a large volume of local anaesthetic in highly vascularised areas, often close to large vessels where there is an increased risk of intravascular injection and/or rapid systemic absorption. This can lead to high plasma concentrations.

Local anaesthetic procedures
Certain local anaesthetic procedures such as injection in the head and neck region, including retrobulbar, dental and stellate ganglion blocks, may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used. The side effects may be similar to the systemic toxicity seen with unintentional intravascular injections of larger doses.

Careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness should be accomplished after each local anaesthetic injection. It should be kept in mind that at such times restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of CNS toxicity.

Local anaesthetics should be given with great caution (if at all) to patients with preexisting abnormal neurological pathology, e.g. myasthenia gravis. Use with extreme caution in epidural, caudal and spinal anaesthesia when there are serious diseases of the CNS or of the spinal cord, e.g. meningitis, spinal fluid block, cranial or spinal haemorrhage, tumours, poliomyelitis, syphilis, tuberculosis or metastatic lesions of the spinal cord.

Anti-arrhythmic drugs
Patients treated with class III anti-arrhythmic drugs (e.g. amiodarone) should be under close surveillance. ECG monitoring should also be considered, since cardiac effects may be additive.

Accidental intravascular administration
Injection should always be made slowly with frequent aspirations to avoid inadvertent intravascular injection which can produce toxic effects.

There have been reports of cardiac arrest during the use of ropicavaine hydrochloride 2 mg/mL solution for infusion 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.

Low molecular weight heparins and heparinoids
Spinal/Epidural haematomas – When neuraxial anaesthesia (epidural/spinal anaesthesia) is employed, patients anti-coagulated or scheduled to be anti-coagulated with low molecular weight heparins or heparinoids are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events is increased by the use of indwelling epidural catheters, traumatic or repeated epidural/spinal puncture, and the concomitant use of drugs affecting haemostasis such as NSAIDs, platelet inhibitors or other anticoagulants. Patients should be frequently monitored for signs and symptoms of neurological impairment.

Epidural and intrathecal anaesthesia
Epidural and intrathecal anaesthesia may lead to hypotension and bradycardia. The risk of such effects can be reduced, e.g. by injecting a vasopressor. Hypotension should be treated promptly with a sympathomimetic, repeated as necessary.

Intra-articular injection
When Ropivacaine-AFT 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.

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 Ropivacaine-AFT.

Cytochrome P450 enzymes
Ropivacaine-AFT should be used with caution in patients with known drug sensitivities and should be avoided in patients treated with strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin (see **Section 4.5 Interaction with other medicines and other forms of interaction**).

Porphyria
Ropivacaine-AFT 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.

Use in hepatic impairment
Ropivacaine is eliminated primarily by hepatic metabolism and changes in hepatic function may have significant consequences. Ropivacaine has an intermediate to low clearance, which depends on its unbound fraction and intrinsic metabolic clearance. Ropivacaine-AFT should therefore be used with caution in patients with severe hepatic disease. Repeated doses may need to be reduced due to delayed elimination.

Use in renal impairment
Normally there is no need to modify the dose in patients with impaired renal function when used for single dose or short-term treatment. Acidosis and reduced plasma protein concentration, frequently seen in patients with chronic renal dysfunction may increase the risk of systemic toxicity (see **4.2 Dose and method of administration**).

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

Paediatric population
Children aged between 0 and 12 years should be given doses commensurate with their weight and clinical status.

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

infusions are to be used in neonates, ropivacaine doses must be individually titrated by a specialist in paediatric anaesthesia. Regular monitoring for systemic toxicity (e.g. by signs of CNS toxicity, ECG, SpO_2) is always required for neonates. Monitoring should be continued after completion of infusion due to decreased rates of elimination of ropivacaine in neonates. Dose recommendations have not been established in premature neonates but organ immaturity would be expected to result in even slower elimination.

4.5. Interactions with other medicines and other forms of interaction

Local anaesthetics and antiarrhythmic drugs
Ropivacaine-AFT 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 toxic effects are additive. Specific interaction studies with Ropivacaine-AFT and class III anti-arrhythmic drugs (e.g. amiodarone) have not been performed, but caution is advised (see **Section 4.4 Special warnings and precautions for use**).

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

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

Cytochrome P450 interactions (see **Section 5.2 Pharmacokinetic properties**)
Ropivacaine is metabolised by the enzymes CYP1A2 and CYP3A4. Interactions with inducers of these enzymes are not expected to be clinically relevant, however there is a potential for metabolic interaction when Ropivacaine-AFT is used in combination with a potent enzyme inhibitor.

CYP1A2 inhibitors
Fluvoxamine
Fluvoxamine is a potent competitive inhibitor of P4501A2. During co-administration of oral fluvoxamine treatment, a 77% decrease in ropivacaine clearance and a 3- fold higher AUC in healthy volunteers was seen. Single administrations of Ropivacaine-AFT should be used with care in patients who are concomitantly receiving a potent CYP1A2 inhibitor (see **Section 4.4 Special warnings and precautions for use**). Repeated administration or long-term infusion should be avoided in such patients.

A theoretical possibility of metabolic drug interactions with potent inhibitors of CYP1A2, such as fluvoxamine and enoxacin, when given concomitantly with Ropivacaine-AFT,

can lead to an increased ropivacaine plasma concentration (see **Section 4.4 Special warnings and precautions for use**).

CYP3A4 inhibitors

Ketoconazole

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

Theoretical interactions

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

Metabolic interactions

With the low to intermediate hepatic extraction ratio of ropivacaine (mean 0.4), a fall in the liver blood flow is not expected to have a significant influence on ropivacaine clearance (see **4.4 Special warnings and precautions for use**).

Clinical relevance of interactions

In the clinical experience with ropivacaine hydrochloride 2 mg/mL solution for infusion, patients usually received ropivacaine hydrochloride 2 mg/mL solution for infusion in combination with several other therapies. The safety evaluation of ropivacaine hydrochloride 2 mg/mL solution for infusion is therefore based upon its use in combination with various concomitant treatments. The review of safety data in these studies show that ropivacaine hydrochloride 2 mg/mL solution for infusion has a safety profile comparable to another amide local anaesthetic used for regional anaesthesia.

These data did not indicate any specific drug interactions that would require special study for the use of ropivacaine hydrochloride 2 mg/mL solution for infusion as a single-dose or for treatment for less than 24 hours. Furthermore, drugs metabolised by CYP1A2, e.g. paracetamol, have also been used in combination with ropivacaine hydrochloride 2 mg/mL solution for infusion in the clinical program, without clinical evidence of metabolic interactions (see **Section 5.2 Pharmacokinetic properties**).

4.6. Fertility, pregnancy and lactation

Use in pregnancy

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

Studies in animals have not shown evidence of an increased occurrence in foetal damage.

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

The epidural use of Ropivacaine-AFT in obstetrics is well documented and adverse effects have been reported (see **Section 4.8 Undesirable effects – paediatric population**).

Intrathecal administration has not been documented for caesarean section.

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

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

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Summary of the safety profile
Adverse events reported in association with Ropivacaine-AFT are similar in character to those observed with other local anaesthetics of the amide type.

Adverse reactions may be due to high plasma levels as a result of excessive dosage, rapid absorption, delayed elimination or metabolism, or inadvertent intravascular injection. They should be distinguished from the physiological effects of the nerve block itself e.g. a decrease in blood pressure and bradycardia during epidural and

intrathecal anaesthesia and events caused by needle puncture (e.g. spinal haematoma, postdural puncture, headache, meningitis and epidural abscess).

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

The effects of systemic overdose and unintentional intravascular injection may involve the central nervous system and/or the cardiovascular system (see **Section 4.9 Overdose**). Inadvertent subarachnoid injection may lead to CNS depression, respiratory arrest and cardiovascular collapse.

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

Tabulated summary of adverse reactions

A large number of adverse events have been reported during clinical development, the majority related to the expected effects of the block and to the clinical situation rather than reactions to the drug. The following adverse events are considered to be of clinical importance regardless of causal relationship.

Adverse medicine reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (> 1/10); common (> 1/100, < 1/10); uncommon (> 1/1,000, < 1/100); rare (> 1/10,000, <1/1,000); very rare (< 1/10,0000); including isolated reports.

Psychiatric disorders:

Common:	Insomnia
Uncommon:	Anxiety

Nervous system disorders:

Common:	Paraesthesia, headache[a], dizziness
Uncommon:	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]

Cardiac disorders:

Common:	Bradycardia[a], tachycardia
Rare:	Cardiac arrest, cardiac arrhythmias

Vascular disorders:

Very common:	Hypotension[c]
Common:	Hypertension
Uncommon:	Syncope[a]

Respiratory, thoracic and mediastinal disorders:

Uncommon: Dyspnoea[a]

Gastrointestinal disorders:

Very common: Nausea

Common: Vomiting[a,d]

Musculoskeletal and connective tissue disorders:

Common: Back pain

Renal and urinary disorders:

Common: Urinary retention[a], oliguria

General disorders and administration site conditions:

Common: Chest pain, pain, temperature elevation, rigors (chills)

Uncommon: Hypothermia[a]

Rare: Allergic reactions (anaphylactoid reactions, angioneurotic oedema and urticaria)

[a] These reactions are more frequent after spinal anaesthesia

[b] These symptoms usually occur because of inadvertent intravascular injection, overdose or rapid absorption (see **Section 4.9 Overdose**)

[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 anaesthetic technique regardless of the local anaesthetic used.

Neurological complications

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

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 vascularized areas (see **Section 4.4 Special warnings and precautions for use**). 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

This 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

Such 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.

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

Adverse medicine reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (> 1/10); common (> 1/100, < 1/10); uncommon (> 1/1,000, < 1/100); rare (> 1/10,000, <1/1,000); very rare (< 1/10,0000); including isolated reports.

Infections and infestations:
Uncommon: Neonatal sepsis

Metabolism and nutrition disorders:
Uncommon: Foetal acidosis and neonatal hypoglycaemia

Cardiac disorders:
Common: Foetal distress, foetal tachycardia and foetal bradycardia

Respiratory, thoracic and mediastinal disorders:
Common: Neonatal respiratory disorders and neonatal tachypnoea

Gastrointestinal disorders:
Common: Neonatal vomiting

Hepatobiliary disorders:
Common: Neonatal jaundice

Musculoskeletal and connective tissue disorders:
Uncommon: Hypotonia

General disorders and administration site conditions:
Common: Neonatal fever
Uncommon: Low Apgar score

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

4.9. Overdose

Acute emergencies associated with the use of local anaesthetics are generally related to high plasma levels or to unintended subarachnoid injection of the local anaesthetic solution (see **Section 4.8 Adverse effects** and **Section 4.4 Special warnings and precautions for use**).

Accidental intravascular injections of local anaesthetics may cause immediate toxic effects. Onset of effects might be within seconds to a few minutes. Toxic effects may also arise from exceptionally rapid absorption from highly vascularised areas, causing systemic toxicity in 15 – 60 minutes. In the event of overdose, peak plasma concentrations may not be reached for one to two hours, depending on the site of the injection and signs of toxicity may thus be delayed. Systemic toxic reactions may involve the central nervous system and the cardiovascular system.

After intrathecal administration, systemic toxicity is expected to be low, due to the low dose administered. However, an excessive dose administered into the intrathecal space may give rise to total spinal block.

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

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

Unconsciousness and grand mal convulsions may follow, which can last from a few seconds to several minutes. Hypoxia and hypercapnia occur rapidly during convulsions due to the increased muscular activity, together with disruption to respiration and possible loss of functional airways. In severe cases apnoea may occur. Respiratory and metabolic acidosis, hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

Recovery follows the redistribution of the local anaesthetic drug from the central nervous system and subsequent metabolism and excretion. Recovery should be rapid unless large amounts of the drug have been injected.

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

signs of depression of conductivity and contractility.

Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anaesthetic or is heavily sedated with drugs such as benzodiazepines or barbiturates. However, in rare cases, cardiac arrest has occurred without prodromal CNS effects.

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

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

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

If cardiovascular depression is evident (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor and or inotropic agents should be considered. Children aged between 0 and 12 years should be given doses commensurate with their age, weight and clinical status.

If ventricular fibrillation, cardiac arrest or circulatory arrest occur, cardiopulmonary resuscitation must be instituted and maintained. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

Should cardiac arrest occur, prolonged resuscitative efforts may be required to improve the possibility of a successful outcome.

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

Pharmacotherapeutic group: Anesthetics, local; ATC code: N01BB09

Mechanism of action
Ropivacaine hydrochloride is a member of the amide class of local anaesthetics and is

supplied as the S-(-)-enantiomer. Ropivacaine has both anaesthetic and analgesic effects. At higher doses it produces surgical anaesthesia with motor block, while at lower doses it produces a sensory block including analgesia with little and non-progressive motor block.

The onset, duration and intensity of the local anaesthetic effect of Ropivacaine-AFT depend of 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.

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.

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

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

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

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

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

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

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

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

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

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

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

In man, ropivacaine is less toxic regarding the CNS and cardiovascular systems than bupivacaine. In two tolerability studies in volunteers given IV infusions, CNS symptoms

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

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

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

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

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

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

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

Four open label, randomised studies were performed to investigate the efficacy and safety of ropivacaine 0.5% (5 mg/mL) and other strengths for intrathecal administration in surgical anaesthesia. A total 224 patients were studied, of which 217 patients were

valid for safety and 212 for efficacy. In two studies, patients underwent minor orthopaedic, gynaecological or urological surgery suited for spinal anaesthesia. In the other two studies, patients underwent a unilateral hip replacement. Ropivacaine 15 – 20 mg administered intrathecally was effective and the anaesthetic quality was rated high by surgeons, anaesthetists and patients. The incidence and severity of adverse events reported were not related to dose.

Paediatric population

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

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

5.2. Pharmacokinetic properties

Ropivacaine has a chiral centre and is the pure S-(-)-enantiomer. Ropivacaine has a pKa 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.

Absorption

Ropivacaine shows complete and biphasic absorption from the epidural space with half-lives of the two phases in the order of 14 minutes and 4 hours. The slow absorption is the rate-limiting factor in the elimination of ropivacaine, which explains why the

apparent elimination half-life is longer after epidural than after intravenous administration. Ropivacaine shows a biphasic absorption from the caudal epidural space also in children.

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

Table 3: The pharmacokinetic profile of ropivacaine in adults

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

Ropivacaine is mainly bound to α_1-acid glycoprotein in plasma with an unbound pharmacologically active fraction of about 6%.

An increase in total plasma concentrations during continuous post-operative epidural infusion and interscalene infusion has been observed. This increase is related to a post-operative increase of α_1-acid glycoprotein. Variations in unbound, i.e. pharmacologically active, concentration of ropivacaine 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 on the foetus.

Metabolism
Ropivacaine is extensively metabolised in the liver, predominantly by aromatic hydroxylation to 3-hydroxy-ropivacaine mediated by cytochrome P4501A2 and N-dealkylation to PPX by CYP3A4. The major metabolite is 3-hydroxy-ropivacaine. After single IV administration this metabolite accounts for about 37% of urinary excretion, mainly as a glucuronide conjugate. The only metabolite which reaches detectable concentrations in plasma is 3-hydroxy-ropivacaine (conjugated and unconjugated). Urinary excretion of 4-hydroxy-ropivacaine, the N-dealkylated metabolite and the 4-hydroxy-dealkylated metabolite accounts for 1 – 3% of a given dose.

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

There is no evidence of in vivo racemization of ropivacaine.

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

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

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

Unbound ropivacaine clearance increases from 2.4 and 3.6 L/h/kg in the newborn and the 1-month neonate to about 8 – 16 L/h/kg for ages above 6 months, values within the range of those in adults. Total ropivacaine clearance values per kg body weight increase from about 0.10 and 0.15 L/h/kg in the newborn and the 1-month neonate to about 0.3 – 0.6 L/h/kg beyond the age of 6 months. Unbound ropivacaine volume of distribution per kg body weight increases from 22 and 26 L/kg in the newborn and the 1-month neonate to 42 – 66 L/kg above 6 months. Total ropivacaine volume of distribution per kg body weight increases from 0.9 and 1.0 L/kg for the newborn and the 1-month neonate to 1.7 – 2.6 L/kg beyond the age of 6 months. The terminal half-life of ropivacaine is longer, 6 to 5 hours in the newborn and the 1-month neonate compared to about 3 hours in older children. The terminal half-life of PPX is also longer, from 43 and 26 hours in the newborn and the 1-month neonate to about 15 hours 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 – 6 months compared to older children which is related to the immaturity of their liver function. However, this is partly compensated for by the recommended 50% lower dose rate for continuous infusion in infants below 6 months.

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

When comparing descriptive data in a trial of caudal/epidural infusions in 10 full term neonates aged 0 – 30 days, to that in 18 older patients aged 31 – 180 days, total and unbound ropivacaine was higher and showed higher inter-individual variability, unbound apparent clearance lower and ropivacaine binding to plasma proteins (AAG) was lower. There was a greater relative excretion of ropivacaine in urine. Plasma concentrations of total and unbound PPX were similar but PPX had a longer half-life. The sum of unbound concentrations of ropivacaine and one twelfth of PPX was higher in neonates 0 – 7 days. While the highest level reached was 0.24 mg/L, this may have been still rising when observations ceased at 72 hours (only 4 observations). The systemic CNS toxicity threshold in adults is 0.34 mg/L in a mature nervous system (see **Section 5.1 Pharmacodynamic properties – Pharmacodynamics and tolerability**). It is not known how immaturity of the CNS affects toxic thresholds.

Foetuses exposed to ropivacaine during labour or caesarean section can be regarded, after they have been born, as neonates with a peak plasma concentration at the time of delivery. The maximum unbound plasma ropivacaine concentrations in the newborn as reflected in the umbilical vein at delivery, 0.03 to 1.11 mg/L, are in the same range as those seen after single caudal block in neonates and support the documentation of ropivacaine in neonates.

Table 4: Neonatal exposure based on umbilical venous plasma concentrations at delivery after epidural block for caesarean section with ropivacaine 115 – 150 mg or continuous lumbar epidural infusion with 25 mg/h in labour.

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

Pharmacokinetics during pregnancy at term

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

Epidural injection

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

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

Epidural infusion

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

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

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

Table 5: Umbilical arterial (UA) and venous (UV) unbound concentrations after continuous lumbar epidural infusion of ropivacaine and bupivacaine 25 mg/h in labour are presented in the following table.

	UA free (mg/L)
Ropivacaine Actual total dose given of ropivacaine HCl 145 – 200 mg	0.027 – 0.058 (n = 4)
Median	**0.036**
Bupivacaine Actual total dose given of bupivacaine HCl 93.5 – 227.4 mg	0.014 – 0.021 (n = 2)
Median	**0.017**
Ropivacaine Actual total dose given of ropivacaine HCl 99.2 – 255.4 mg	0.027 – 0.067 (n = 10)
Median	**0.042**
Bupivacaine Actual total dose given of ropivacaine HCl 93.5 – 365.3 mg	0.011 – 0.035 (n = 9)
Median	**0.025**

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 (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)
Water for injections

6.2. Incompatibilities

Ropivacaine-AFT solution for infusion in plastic infusion bags is chemically and physically compatible with fentanyl citrate, sufentanil citrate, morphine sulphate and clonidine hydrochloride.

Table 6: Compatibility of Ropivacaine-AFT

Concentration of ROPIVACAINE 2 mg/mL (0.2%)	
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

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

Alkaline solutions
The solubility of ropivacaine is limited at pH values above 6.0. This must be taken into consideration if adding alkaline solutions (e.g. carbonates), since precipitation might occur at higher pH values.

6.3. Shelf life

Ropivacaine-AFT has a shelf life of 24 months from the date of manufacture.

6.4. Special precautions for storage

Store below 25 ˚C. Do not refrigerate. Do not freeze.

6.5. Nature and contents of container

Ropivacaine-AFT 2 mg/mL (0.2%) are presented in 100 mL and 200 mL polyolefin bags with 2 ports in an over bag.

Each carton contains 10 bags.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal

The presentations of Ropivacaine-AFT infusion solution contain no antimicrobial preservative and are intended for single use only. Any solution remaining from an opened container should be discarded. (see **Section 6.2 Incompatibilities**).

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

31 May 2022

10. DATE OF REVISION

July 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
3 and 4.2	Typographic errors corrected