Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ropivacaine 2 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml solution for injection contains 2 mg ropivacaine hydrochloride.
Each 10 ml ampoule contains 20 mg ropivacaine hydrochloride.
Each 20 ml ampoule contains 40 mg ropivacaine hydrochloride.

Excipient with known effect:
Each 10 ml ampoule contains 1.48 mmol (or 34 mg) of sodium.
Each 20 ml ampoule contains 2.96 mmol (or 68 mg) of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution with a pH of 4.0 to 6.0 and an osmolality between 255 and 305 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ropivacaine 2 mg/ml solution for injection is indicated for acute pain management:

- In adults and children above 12 years of age for

- Continuous epidural infusion or intermittent bolus administration during postoperative or labour pain
- Field blocks
- Continuous peripheral nerve block via a continuous infusion or intermittent bolus injections, e.g. postoperative pain management

- In infants from 1 year and children up to and including 12 years of age for:

- Single and continuous peripheral nerve block

- In neonates, infants and children up to and including 12 years for (per- and postoperative)

- Caudal epidural block
- Continuous epidural infusion

4.2 Posology and method of administration

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

Posology

Ropivacaine 2 mg/ml solution for injection

Adults and adolescents above 12 years of age

The following table 1 is a guide to dosage for the more commonly used blocks. The smallest dose required to produce an effective block should be used. The clinician's experience and knowledge of the patient's physical status are of importance when deciding the dose.

Table 1Adults and adolescents above 12 years of age

	Concentration mg/ml	Volume ml	Dose mg	Onset minutes	Duration hours
ACUTE PAIN MANAGEMENT					
Lumbar Epidural Administration					
Bolus	2.0	10-20	20-40	10-15	0.5-1.5
Intermittent injections (top-up) (e.g. labour pain management)	2.0	10-15 (minimum interval 30 minutes)	20-30		
Continuous infusion e.g. labour pain	2.0	6-10 ml/h	12-20 mg/h	n/a	n/a
Postoperative pain management	2.0	6-14 ml/h	12-28 mg/h	n/a	n/a
Thoracic Epidural Administration					
Continuous infusion (postoperative pain management)	2.0	6-14 ml/h	12-28 mg/h	n/a	n/a
Field Block					
(e.g. minor nerve blocks and infiltration)	2.0	1-100	2.0-200	1-5	2-6
Peripheral nerve block (Femoral or interscalene block)					
Continuous infusion or intermittent injections (e.g. postoperative pain management)	2.0	5-10 ml/h	10-20 mg/h	n/a	n/a

The doses in the table are those considered to be necessary to produce a successful block and should be regarded as guidelines for use in adults. Individual variations in onset and duration occur. The figures in the column 'Dose' reflect the expected average dose range needed. Standard textbooks should be consulted for both factors affecting specific block techniques and individual patient requirements.
n/a = not applicable

Method of administration

Careful aspiration before and during injection is recommended to prevent intravascular injection. When a large dose is to be injected, a test dose of 3-5 ml lidocaine (lignocaine) with adrenaline (epinephrine) is recommended. An inadvertent intravascular injection may be recognised by a temporary increase in heart rate and an accidental intrathecal injection by signs of a spinal block.

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

When prolonged blocks are used, either through continuous infusion or through repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. Cumulative doses up to 675 mg ropivacaine for surgery and postoperative analgesia administered over 24 hours were well tolerated in adults, as were postoperative continuous epidural infusions at rates up to 28 mg/hour for 72 hours. In a limited number of patients higher doses of up to 800 mg/day have been administered with relatively few adverse reactions.

For treatment of postoperative pain, the following technique can be recommended: Unless preoperatively instituted, an epidural block with Ropivacaine Kabi 7.5 mg/ml is induced via an epidural catheter. Analgesia is maintained with Ropivacaine Kabi 2 mg/ml infusion. Infusion rates of 6-14 ml (12-28 mg), per hour provide adequate analgesia with only slight and non-progressive motor block in most cases of moderate to severe postoperative pain. The maximum duration of epidural block is 3 days. However, close monitoring of analgesic effect should be performed in order to remove the catheter as soon as the pain condition allows it. With this technique a significant reduction in the need for opioids has been observed.

In clinical studies an epidural infusion of ropivacaine 2 mg/ml alone or mixed with fentanyl 1-4 µg/ml has been given for postoperative pain management for up to 72 hours. The combination of ropivacaine and fentanyl provided improved pain

relief but caused opioid side effects. The combination of ropivacaine and fentanyl has been investigated only for ropivacaine 2 mg/ml.

When prolonged peripheral nerve blocks are applied, either through continuous infusion or through repeated injections, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. In clinical studies, femoral nerve block was established with 300 mg ropivacaine 7.5 mg/ml and interscalene block with 225 mg ropivacaine 7.5 mg/ml, 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.

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

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 (see section 4.4. and 5.2).

Hepatic impairment
Ropivacaine is metabolised in the liver and should therefore be used with caution in patients with severe liver disease. Repeated doses may need to be reduced due to delayed elimination (see section 4.4. and 5.2).

Paediatric population

Table 2Epidural Block: Paediatric patients from 0 (term neonates) up to and including 12 years of age

	Concentration mg/ml	**Volume ml/kg**	**Dose mg/kg**
ACUTE PAIN MANAGEMENT (per- and postoperative)			
Single Caudal Epidural Block			
Blocks below T12, in children with a body weight up to 25 kg	2.0	1	2
Continuous Epidural Infusion			
In children with a body weight up to 25 kg			
0 up to 6 months			
Bolus dose[a]	2.0	0.5-1	1-2
Infusion up to 72 hours	2.0	0.1 ml/kg/h	0.2 mg/kg/h
6 up to12 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

The dose in the table should be regarded as guidelines for use in paediatrics. Individual variations occur. In children with a high body weight, a gradual reduction of the dosage is often necessary and should be based on the ideal body weight. The volume for single caudal epidural block and the volume for epidural bolus doses should not exceed 25 mL in any patient. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.
[a] Doses in the low end of the dose interval are recommended for thoracic epidural blocks while doses in the high end are recommended for lumbar or caudal epidural blocks.
[b] Recommended for lumbar epidural blocks. It is good practice to reduce the bolus dose for thoracic epidural analgesia

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

Table 3Peripheral nerve blocks: Infants and children aged 1-12 years	**Concentration mg/ml**	**Volume ml/kg**	**Dose mg/kg**
ACUTE PAIN MANAGEMENT (per- and postoperative)			
Single injections for peripheral nerve block			
e.g. ilioinguinal nerve block, brachial plexus block, fascia iliaca compartment block	2.0	0.5 – 0.75	1.0 – 1.5

Multiple blocks	2.0	0.5 – 1.5	1.0 – 3.0
Continuous infusion for peripheral nerve block in children 1 to 12 years			
Infusion up to 72 hours	2.0	0.1 – 0.3 ml/kg/h	0.2 – 0.6 mg/kg/h

The dose in the table should be regarded as guidelines for use in paediatrics. Individual variations occur. In children with a high body weight a gradual reduction of the dosage is often necessary and should be based on the ideal body weight. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

Single injections for peripheral nerve block (e.g. ilioinguinal nerve block, brachial plexus block, fascia iliaca compartment block) should not exceed 2.5-3.0 mg/kg.

The doses for peripheral block in infants and children provide guidance for use in children without severe disease. More conservative doses and close monitoring are recommended for children with severe diseases.

Method of administration

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

A single caudal epidural injection of ropivacaine 2 mg/ml produces adequate postoperative analgesia below T12 in the majority of patients when a dose of 2 mg/kg is used in a volume of 1 ml/kg. The volume of the caudal epidural injection may be adjusted to achieve a different distribution of sensory block, as recommended in standard textbooks. In children above 4 years of age, doses up to 3 mg/kg of a concentration of ropivacaine 3 mg/ml have been studied. However, this concentration is associated with a higher incidence of motor block.

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

In case infusion of ropivacaine is recommended, Ropivacaine Kabi solution for infusion can be used.

Ropivacaine Kabi 7.5 mg/ml and Ropivacaine Kabi 10 mg/ml solution for injection

Adults and adolescents above 12 years of age

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

	Concentration mg/ml	Volume ml	Dose mg	Onset minutes	Duration hours
SURGICAL ANAESTHESIA					
Lumbar Epidural Administration					
Surgery	7.5	15-25	113-188	10-20	3-5
	10.0	15-20	150-200	10-20	4-6
Caesarean section	7.5	15-20	113-150[1)]	10-20	3-5
Thoracic Epidural Administration					
To establish block for post-operative pain relief	7.5	5-15 (dependent on the level of injection)	38-113	10-20	n/a[2)]
Major Nerve Block*					
Brachial plexus block	7.5	30-40	225-300[3)]	10-25	6-10
Field Block					
(e.g. minor nerve blocks and infiltration)	7.5	1-30	7.5-225	1-15	2-6

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

* With regard to major nerve block, only for brachial plexus block a dose recommendation can be given. For other major nerve blocks lower doses may be required. However, there is presently no experience of specific dose recommendations for other blocks.
1) Incremental dosing should be applied, the starting dose about 100 mg (97.5 mg = 13 ml; 105 mg = 14 ml) to be given over 3-5 minutes. Two extra doses, in total an additional 50mg, may be administered as needed.
2) n/a = not applicable
3) The dose for a major nerve block must be adjusted according to site of administration and patient status. Interscalene and supraclavicular brachial plexus blocks may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used, (see section 4.4).

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

Method of administration

Careful aspiration before and during injection is recommended to prevent intravascular injection. When a large dose is to be injected, a test dose of 3-5 ml lidocaine (lignocaine) with adrenaline (epinephrine) is recommended. An inadvertent intravascular injection may be recognised by a temporary increase in heart rate and an accidental intrathecal injection by signs of a spinal block.

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

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

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

When prolonged blocks are used, either through continuous infusion or through repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. Cumulative doses up to 675 mg ropivacaine for surgery and postoperative analgesia administered over 24 hours were well tolerated in adults, as were postoperative continuous epidural infusions at rates up to 28 mg/hour for 72 hours. In a limited number of patients higher doses of up to 800 mg/day have been administered with relatively few adverse reactions.

For treatment of postoperative pain, the following technique can be recommended: Unless preoperatively instituted, an epidural block with Ropivacaine Kabi 7.5 mg/ml is induced via an epidural catheter. Analgesia is maintained with Ropivacaine Kabi 2 mg/ml infusion. Infusion rates of 6-14 ml (12-28 mg), per hour provide adequate analgesia with only slight and non-progressive motor block in most cases of moderate to severe postoperative pain. The maximum duration of epidural block is 3 days. However, close monitoring of analgesic effect should be performed in order to remove the catheter as soon as the pain condition allows it. With this technique a significant reduction in the need for opioids has been observed.

In clinical studies an epidural infusion of ropivacaine 2 mg/ml alone or mixed with fentanyl 1-4 µg/ml has been given for postoperative pain management for up to 72 hours. The combination of ropivacaine and fentanyl provided improved pain relief but caused opioid side effects. The combination of ropivacaine and fentanyl has been investigated only for ropivacaine 2 mg/ml.

When prolonged peripheral nerve blocks are applied, either through continuous infusion or through repeated injections, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. In clinical studies, femoral nerve block was established with 300 mg ropivacaine 7.5 mg/ml and interscalene block with 225 mg ropivacaine 7.5 mg/ml, 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.

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

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 (see section 4.4. and 5.2).

Hepatic impairment
Ropivacaine is metabolised in the liver and should therefore be used with caution in patients with severe liver disease. Repeated doses may need to be reduced due to delayed elimination (see section 4.4. and 5.2).

Paediatric population

Paediatric patients from 0 (term neonates) up to and including 12 years of age
The use of Ropivacaine 7.5 and 10 mg/ml may be associated with systemic and central toxic events in children. Lower strengths (2 mg/ml, 5 mg/ml) are more appropriate for administration in this population.

4.3 Contraindications

- Hypersensitivity to ropivacaine or to other local anaesthetics of the amide type, or to any of the excipients listed in section 6.1
- General contraindications related to epidural anesthesia, regardless of the local anaesthetic used, should be taken into account
- Intravenous regional anaesthesia
- Obstetric paracervical anaesthesia
- Hypovolaemia

4.4 Special warnings and precautions for use

Regional anaesthetic procedures should always be performed in a properly equipped and staffed area. Equipment and medicinal products necessary for monitoring and emergency resuscitation should be immediately available.

Patients receiving major blocks should be in an optimal condition and have an intravenous line inserted before the blocking procedure.

The clinician responsible should take the necessary precautions to avoid intravascular injection (see section 4.2) and be appropriately trained and familiar with diagnosis and treatment of undesirable effects, systemic toxicity and other complications (see section 4.8 and 4.9) such as inadvertent subarachnoid injection which may produce a high spinal block with apnoea and hypotension. Convulsions have occurred most often after brachial plexus block and epidural block. This is likely to be the result of either accidental intravascular injection or rapid absorption from the injection site.

Caution is required to prevent injections in inflamed areas.

Cardiovascular effects
Epidural and intrathecal anaesthesia may lead to hypotension and bradycardia. Hypotension should be treated promptly with a vasopressor intravenously, and with an adequate vascular filling. Patients treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive (see section 4.5). There have been rare reports of cardiac arrest during the use of ropivacaine for epidural anaesthesia or peripheral nerve blockade, especially after unintentional intravascular administration in elderly patients and in patients with concomitant heart disease. In some instances, resuscitation has been difficult. Should cardiac arrest occur, prolonged resuscitative efforts may be required to improve the possibility of a successful outcome.

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

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

Hypersensitivity
A possible cross – hypersensitivity with other amide – type local anaesthetics should be taken into account (see section 4.3).

Hypovolaemia
Patients with hypovolaemia due to any cause can develop sudden and severe hypotension during epidural anaesthesia, regardless of the local anaesthetic used (see section 4.3).

Patients in poor general health
Patients in poor general condition due to ageing or other compromising factors such as partial or complete heart conduction block, advanced liver disease or severe renal dysfunction require special attention, although regional anaesthesia is frequently indicated in these patients.

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

Acute porphyria
Ropivacaine solution for injection is possibly porphyrinogenic and should only be prescribed to patients with acute porphyria when no safer alternative is available. Appropriate precautions should be taken in the case of vulnerable patients, according to standard text books and/or in consultation with disease area experts.

Chondrolysis
There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics, including ropivacaine. The majority of reported cases of chondrolysis have involved the shoulder joint. Intra-articular continuous infusion is not an approved indication for ropivacaine. Intra-articular continuous infusion with Ropivacaine should be avoided, as the efficacy and safety has not been established.

Excipients with recognised action/effect
Ropivacaine 2 mg/ml:
This medicinal product contains 3.4 mg sodium per ml, equivalent to 0.17% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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

Paediatric population
Ropivacaine 2 mg/ml:
Neonates may need special attention due to immaturity of metabolic pathways. The larger variations in plasma concentrations of ropivacaine observed in clinical trials in neonates suggest that there may be an increased risk of systemic toxicity in this age group, especially during continuous epidural infusion. The recommended doses in neonates are based on limited clinical data. When ropivacaine is used in this patient group, regular monitoring of systemic toxicity (e.g. by signs of CNS toxicity, ECG, SpO_2) and local neurotoxicity (e.g. prolonged recovery) is required, which should be continued after ending infusion, due to a slow elimination in neonates.

- The safety and efficacy of ropivacaine 2 mg/ml for field block in children up to and including 12 years has not been established.

- The safety and efficacy of ropivacaine 2 mg/ml for peripheral nerve blocks in infants below 1 year has not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Ropivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, e.g., certain antiarrhythmics, such as lidocaine and mexiletine, since the systemic toxic effects are additive. Simultaneous use of Ropivacaine with general anaesthetics or opioids may potentiate each other's (adverse) effects. Specific interaction studies with ropivacaine and anti-arrhythmic drugs class III (e.g., amiodarone) have not been performed, but caution is advised (see also section 4.4).

Cytochrome P450 (CYP) 1A2 is involved in the formation of 3-hydroxy ropivacaine, the major metabolite.

In vivo the plasma clearance of ropivacaine was reduced by up to 77 % during co-administration of fluvoxamine, a selective and potent CYP1A2 inhibitor. Thus strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin, given concomitantly during prolonged administration of Ropivacaine, can interact with ropivacaine. Prolonged administration of ropivacaine should be avoided in patients concomitantly treated with strong CYP1A2 inhibitors (see section 4.4).

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

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

4.6 Fertility, pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Depending on the dose, local anaesthetics may have a minor influence on mental function and coordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

General

The adverse reaction profile for Ropivacaine Kabi is similar to those for other long acting local anaesthetics of the amide type. Adverse drug reactions should be distinguished from the physiological effects of the nerve block itself e.g. hypotension and bradycardia during spinal/epidural block, and events caused by needle puncture (e.g., spinal haematoma, postdural puncture headache, meningitis and epidural abscess).

The most frequently reported adverse reactions, nausea and hypotension, are very frequent during anaesthesia and surgery in general and it is not possible to distinguish those caused by the clinical situation from those caused by the medicinal product or the block.

The percentage of patients that can be expected to experience adverse reactions varies with the route of administration of Ropivacaine Kabi. Systemic and localised adverse reactions of ropivacaine usually occur because of excessive dosage, rapid absorption, or inadvertent intravascular injection.

Table 4 Tabulated list of adverse reactions

The frequencies used in the table 4 in Section 4.8 are: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to < 1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Undesirable effect
Immune system disorders	Rare	Allergic reactions (anaphylactic reactions, anaphylactic shock, angioneurotic oedema and urticaria)
Psychiatric disorders	Uncommon	Anxiety
Nervous system disorders	Common	Paraesthesia, Dizziness, Headache
	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)*, Hypoaesthesia
	Not known	Dyskinesia, Horner's Syndrome
Cardiac disorders	Common	Bradycardia, Tachycardia
	Rare	Cardiac arrest, Cardiac arrhythmias
Vascular disorders	Very common	Hypotension[a]
	Common	Hypertension
	Uncommon	Syncope
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting[b]
Musculoskeletal and connective tissue disorders	Common	Back pain
Renal and urinary disorders	Common	Urinary retention
General disorders and administration site conditions	Common	Temperature elevation, Rigor, Chills
	Uncommon	Hypothermia

[a] Hypotension is less frequent in children (>1/100 to <1/10).
[b] Vomiting is morefrequent in children. (>1/10).
*These symptoms usually occur because of inadvertent intravascular injection, overdose or rapid absorption, see section 4.9.

Description of selected adverse reactions

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

Following epidural administration, cranial spread of local anaesthetic especially in pregnant women may occasionally result in Horner's syndrome characterised by miosis, ptosis, and anhidrosis. Spontaneous resolution occurs upon discontinuation of treatment.

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

Acute systemic toxicity
Systemic toxic reactions primarily involve the central nervous system (CNS) and the cardiovascular system (CVS). Such reactions are caused by high blood concentration of a local anaesthetic, which may appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularised areas, see also section 4.4. CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively.

Central nervous system toxicity
Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. Initially symptoms such as visual or hearing disturbances, perioral numbness, dizziness, light-headedness, tingling and paraesthesia are seen. Dysarthria, muscular rigidity and muscular twitching are more serious and may precede the onset of generalised convulsions. These signs must not be mistaken for neurotic behaviour. Unconsciousness and grand mal convulsions may follow, which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly during convulsions due to the increased muscular activity, together with the interference with respiration. In severe cases even apnoea may occur. The respiratory and metabolic acidosis increases and extends the toxic effects of local anaesthetics.

Recovery follows the redistribution of the active substance from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the medicinal product have been injected.

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

Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anaesthetic or is heavily sedated with medicinal products such as benzodiazepines or barbiturates.

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults except for hypotension which happens less often in children (> 1 in 100 to < 1 in 10) and vomiting which happens more often in children (> 1 in 10).

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

Treatment of acute systemic toxicity
See section 4.9.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product 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 via the HPRA Pharmacovigilance
Website: www.hpra.ie.

4.9 Overdose

Symptoms
Accidental intravascular injections of local anaesthetics may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, peak plasma concentrations may not be reached for one to two hours, depending on the site of the injection, and signs of toxicity may thus be delayed (see section 4.8. "*Acute systemic toxicity*", "*Central nervous system toxicity*" and "*Cardiovascular system toxicity*").

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

If circulatory arrest should occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.
If cardiovascular depression occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, and/or inotropic agents should be considered. Children should be given doses commensurate with age and weight.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, local, Amides, ATC code: N01BB09

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

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

The most characteristic property of ropivacaine is the long duration of action. Onset and duration of the local anaesthetic efficacy are dependent upon the administration site and dose, but are not influenced by the presence of a vasoconstrictor (e.g. adrenaline (epinephrine)). For details concerning the onset and duration of action of Ropivacaine Kabi, see section 4.2 (Table 1).

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

5.2 Pharmacokinetic properties

Absorption and distribution

Ropivacaine has a chiral center and is available as the pure S-(-)-enantiomer. It is highly lipid-soluble. All metabolites have a local anaesthetic effect but of considerably lower potency and shorter duration than that of ropivacaine.

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

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

Ropivacaine shows complete and biphasic absorption from the epidural space with half-lives of the two phases of the order of 14 min and 4 h in adults. The slow absorption is the rate-limiting factor in the elimination of ropivacaine, which explains why the apparent elimination half-life is longer after epidural than after intravenous administration. Ropivacaine shows a biphasic absorption from the caudal epidural space also in paediatric patients.

Ropivacaine has a mean total plasma clearance in the order of 440 ml/min, a renal clearance of 1 ml/min, a volume of distribution at steady state of 47 litres and a terminal half-life of 1.8 h after intravenous administration. Ropivacaine has an intermediate hepatic extraction ratio of about 0.4. It is mainly bound to α_1-acid glycoprotein in plasma with an unbound fraction of about 6 %.

An increase in total plasma concentrations during continuous epidural and interscalene infusion has been observed, related to a postoperative increase of α_1-acid glycoprotein.

Variations in unbound, i.e. pharmacologically active, concentration have been much less than in total plasma concentration.

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

Ropivacaine readily crosses the placenta and equilibrium in regard to unbound concentration will be rapidly reached. The degree of plasma protein binding in the foetus is less than in the mother, which results in lower total plasma concentrations in the foetus than in the mother.

Biotransformation and elimination

Ropivacaine is extensively metabolised, predominantly by aromatic hydroxylation. In total 86 % of the dose is excreted in the urine after intravenous administration of which only about 1 % relates to unchanged drug. The major metabolite is 3-hydroxy-ropivacaine, about 37 % of which is excreted in the urine, mainly conjugated. Urinary excretion of 4-hydroxy-ropivacaine, the N-dealkylated metabolite (PPX) and the 4-hydroxy-dealkylated metabolite accounts for 1- 3 %. Conjugated and unconjugated 3-hydroxy-ropivacaine shows only barely detectable concentrations in plasma.

A similar pattern of metabolites has been found in paediatric patients above one year compared to adults.

Impaired renal function has little or no influence on ropivacaine pharmacokinetics. The renal clearance of PPX is significantly correlated with creatinine clearance. A lack of correlation between total exposure, expressed as AUC, with creatinine clearance indicates that the total clearance of PPX includes a non-renal elimination in addition to renal excretion. Some patients with impaired renal function may show an increased exposure to PPX resulting from a low non-renal clearance. Due to the reduced CNS toxicity of PPX as compared to ropivacaine the clinical consequences are considered negligible in short-term treatment. Patients with end-stage renal disease undergoing dialysis have not been studied.

Paediatric population

The pharmacokinetics of ropivacaine was characterised in a pooled population PK analysis on data in 192 children between 0 and 12 years. Unbound ropivacaine and PPX clearance and ropivacaine unbound volume of distribution depend on both body weight and age up to the maturity of liver function, after which they depend largely on body weight. The maturation of unbound ropivacaine clearance appears to be complete by the age of 3 years, that of PPX by the age of 1 year and unbound

ropivacaine volume of distribution by the age of 2 years. The PPX unbound volume of distribution only depends on body weight. As PPX has a longer half-life and a lower clearance, it may accumulate during epidural infusion.

Unbound ropivacaine clearance (Cl_u) for ages above 6 months has reached values within the range of those in adults. Total ropivacaine clearance (Cl) values displayed in the Table 5 below are those not affected by the postoperative increase in AAG.

Table 5 Estimates of pharmacokinetic parameters derived from the pooled paediatric population PK analysis

Age Group	BW[a] kg	Clu[b] (l/h/kg)	Vu[c] (l/kg)	Cl[d] (l/h/kg)	$t_{1/2}$[e] (h)	$t_{1/2ppx}$[f] (h)
Newborn	3.27	2.40	21.86	0.096	6.3	43.3
1 m	4.29	3.60	25.94	0.143	5.0	25.7
6 m	7.85	8.03	41.71	0.320	3.6	14.5
1 y	10.15	11.32	52.60	0.451	3.2	13.6
4 y	16.69	15.91	65.24	0.633	2.8	15.1
10 y	32.19	13.94	65.57	0.555	3.3	17.8

[a] Median bodyweight for respective age from WHO database.
[b] Unbound ropivacaine clearance
[c] Ropivacaine unbound volume of distribution
[d] Total ropivacaine clearance
[e] Ropivacaine terminal half life
[f] PPX terminal half life

The simulated mean unbound maximal plasma concentration (Cu_{max}) after a single caudal block tended to be higher in neonates and the time to Cu_{max} (t_{max}) decreased with an increase in age (Table 6). Simulated mean unbound plasma concentrations at the end of a 72 h continuous epidural infusion at recommended dose rates also showed higher levels in neonates as compared to those in infants and children. See also section 4.4.

Table 6 Simulated mean and observed range of unbound Cu_{max} after a single caudal block

Age group	Dose (mg/kg)	Cu_{max}[a] (mg/l)	t_{max}[b] (h)	Cu_{max}[c] (mg/l)
0-1 m	2.00	0.0582	2.00	0.05-0.08 (n=5)
1-6 m	2.00	0.0375	1.50	0.02-0.09 (n=18)
6-12 m	2.00	0.0283	1.00	0.01-0.05 (n=9)
1-10 y	2.00	0.0221	0.50	0.01-0.05 (n=60)

[a] Unbound maximal plasma concentration
[b] Time to unbound maximal plasma concentration
[c] Observed and dose-normalised unbound maximal plasma concentration

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

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

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 1- to 12-year-old infants and children receiving 3 mg/kg single peripheral (ilioinguinal) nerve block the median unbound peak concentration reached after 0.8 h is 0.0347 mg/L, one-tenth of the toxicity threshold (0.34 mg/L). The upper 90 % confidence interval for the maximum unbound plasma concentration is 0.074 mg/L, one-fifth of the toxicity threshold. Similarly, for continuous peripheral block (0.6 mg ropivacaine/kg for 72 h) preceded by a 3 mg/kg single peripheral nerve block, the median unbound peak concentration is 0.053 mg/L. The upper 90 % confidence interval for the maximum unbound plasma concentration is 0.088 mg/L, one-quarter of the toxicity threshold.

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

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
In alkaline solutions precipitation may occur as ropivacaine shows poor solubility at pH > 6.0.

6.3 Shelf life

Shelf-life before opening:3 years

Shelf-life after opening:To be used immediately.

6.4 Special precautions for storage

This medicinal product does not require any special storage.

6.5 Nature and contents of container

10 ml transparent polypropylene ampoule.
20 ml transparent polypropylene ampoule.

The polypropylene ampoules are specially designed to fit Luer lock and Luer fit syringes.

Pack sizes:
1, 5, 10 ampoule(s) in blister pack
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling
Ropivacaine products are intended for single use only. Discard any unused solution.
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 intact container must not be re-autoclaved.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kroener Strasse 1
Bad Homburg v.d.H 61352
Germany

8 MARKETING AUTHORISATION NUMBER

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