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(s) with known effect:
Each 10 ml ampoule contains 1.47 mmol (or 33.9 mg) of sodium.
Each 20 ml ampoule contains 2.95 mmol (or 67.8 mg) of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
Clear, colourless, sterile, isotonic, isobaric aqueous solution for injection with a pH of 4.0 to 6.0.

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 :

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

Posology
Adults and children above 12 years of age
The following table is a guide to dosage for the more commonly used blocks. The smallest dose required to produce an effective block should be used. The clinician's experience and knowledge of the patient's physical status are of importance when deciding the dose.

Indication	Concentration	Volume	Dose	Onset	Duration

	mg/ml	ml	mg	minutes	hours
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	--	--
Postoperative pain management	2.0	6-14 ml/h	12-28 mg/h	--	--
Thoracic Epidural Administration					
Continuous infusion (postoperative pain management)	2.0	6-14 ml/h	12-28 mg/h	--	--
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	--	--
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.					

In general, surgical anaesthesia (e.g. epidural administration) requires the use of the higher concentrations and doses. The Ropivacaine 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
Perineural and epidural administration by injection.

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 2% (lignocaine) with adrenaline (epinephrine) 1:200.000 is recommended. An inadvertent intravascular injection may be recognised by a temporary increase in heart rate and an accidental intrathecal injection by signs of a spinal block.

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

In epidural block for surgery, single doses of up to 250 mg ropivacaine hydrochloride 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 hydrochloride 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 7.5 mg/ml is induced via an epidural catheter. Analgesia is maintained with Ropivacaine 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 hydrochloride 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 hydrochloride and fentanyl provided improved pain relief but caused opioid side effects. The combination of ropivacaine hydrochloride and fentanyl has been investigated only for ropivacaine hydrochloride 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 hydrochloride 7.5 mg/ml and interscalene block with 225 mg ropivacaine hydrochloride 7.5 mg/ml, respectively, before surgery. Analgesia was then maintained with ropivacaine hydrochloride 2 mg/ml. Infusion rates or intermittent injections of 10-20 mg per hour for 48 hours provided adequate analgesia and were well tolerated.

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 hydrochloride 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 patients 0 up to and including 12 years of age

Indication	Concentration mg/ml	Volume ml/kg	Dose mg/kg
Single Caudal Epidural Block	2.0	1	2
Blocks below T12, in children with a body weight up to 25 kg			
Continuous epidural infusion In children with a body weight up to 25 kg			
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 ml/kg/h
6 up 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 ml/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 ml/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 text books should be consulted for factors affecting specific block techniques and for individual patient requirements.

a Doses at the low end of the dose intervals 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.

Infants and children aged 1-12 years :
The proposed ropivacaine doses for peripheral block in infants and children provide guidelines for use in children without severe disease. More conservative doses and close monitoring are recommended for children with severe disease.

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

Continuous infusion for peripheral nerve block are recommended at 0.2 - 0.6 mg/kg/h (0,1-0, 3 ml/kg/h) up to 72 h.

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

Method of administration
Epidural administration by injection.

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 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 hydrochloride 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 hydrochloride is recommended, Ropivacaine solution for infusion can be used.

4.3 Contraindications

- Hypersensitivity to the active substance, 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
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 hydrochloride for epidural anaesthesia or peripheral nerve blockade, especially after accidental intravascular administration in elderly patients and in patients with concomitant heart disease. In some instances, resuscitation has been difficult. Should cardiac arrest occur, prolonged resuscitative efforts may be required to improve the possibility of a successful outcome.

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

Major peripheral nerve 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 condition
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, however, regional anaesthesia is frequently indicated in these patients.

Patients with renal and hepatic impairment
Ropivacaine hydrochloride 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 intraarticular 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.

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

Paediatric patients
Neonates may need special attention due to immaturity of metabolic pathways. The larger variations in plasma concentrations of ropivacaine hydrochloride 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 hydrochloride 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 2mg/ml for peripheral nerve blocks in infants below 1 year have not been established.
The safety and efficacy of ropivacaine 2mg/ml for field blocks in children up to and including 12 years has not been established.

Ropivacaine 2mg/ml :
This medicinal product contains 0.147 mmol (or 3.39 mg) sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Ropivacaine hydrochloride 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 hydrochloride and antiarrhythmic drugs class III (e.g., amiodarone) have not been performed, but caution is advised (see 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 hydrochloride was reduced by up to 77% during coadministration of fluvoxamine, a selective and potent CYP1A2 inhibitor. Thus strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin, given concomitantly during prolonged administration of Ropivacaine, can interact with ropivacaine hydrochloride. Prolonged administration of ropivacaine hydrochloride should be avoided in patients concomitantly treated with strong CYP1A2 inhibitors (see section 4.4).

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

In vitro, ropivacaine hydrochloride 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

Fertility
There are no data available concerning the fertility.

Pregnancy
Apart from epidural administration for obstetrical use, there are no adequate data on the use of ropivacaine hydrochloride in 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 hydrochloride 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

The adverse reaction profile for Ropivacaine 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, vomiting 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. Systemic and localised adverse reactions of Ropivacaine usually occur because of excessive dosage, rapid absorption, or inadvertent intravascular injection.

The frequency of undesirable effects listed below is defined using the following convention:
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), Not known (cannot be estimated from the available data).

Psychiatric disorders:	
Uncommon:	Anxiety
Nervous system disorders:	
Common:	Headache, paraesthesia, 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)*, hypoaesthesia
Not known:	Dyskinesia
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]

Renal and urinary disorders:

Common:	Urinary retention

General disorders and administration site conditions:

Common:	Hyperthermia, chills
Uncommon:	Hypothermia

Immune System Disorders

Rare	Allergic reactions (anaphylactic reactions, angioneurotic oedema and urticaria)

Musculoskeletal and Connective Tissue

Common: Back pain

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

Class-related 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.

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 section 4.4). CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the active substance, both quantitatively and qualitatively.

Central nervous system
Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. Initially symptoms such as visual or auditory 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 an underlying neurological disease. Unconsciousness and tonic-clonic (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 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 hydrochloride 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 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
HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms of overdose
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*” and “*Cardiovascular toxicity*”).

Treatment of overdose
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 hydrochloride is a long-acting amide-type local anaesthetic with both anaesthetic and analgesic effects. At high doses ropivacaine hydrochloride 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 hydrochloride is the long duration of action. Onset and duration of the local anaesthetic efficacy are dependant upon the administration site and dose, but are not influenced by the presence of a vasoconstrictor (e.g. epinephrine). For details concerning the onset and duration of action of Ropivacaine (see section 4.2).

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

5.2 Pharmacokinetic properties

Absorption and distribution

Ropivacaine hydrochloride has a chiral centre 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 hydrochloride.

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

Ropivacaine hydrochloride 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 hydrochloride, which explains why the apparent elimination half-life is longer after epidural than after intravenous administration. Ropivacaine hydrochloride shows a biphasic absorption from the caudal epidural space also in paediatric patients.

Ropivacaine hydrochloride 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 hydrochloride has an intermediate hepatic extraction ratio of about 0.4. It is mainly bound to α1-acid glycoprotein in plasma with an unbound fraction of about 6%.

An increase in total plasma concentrations during continuous epidural infusion has been observed, related to a postoperative increase of α1-acid glycoprotein.

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

Since ropivacaine hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride 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 ropivacaine hydrochloride. 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.

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

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

Paediatric patients
The pharmacokinetics of ropivacaine hydrochloride was characterised in a pooled population PK analysis on data in 192 children between 0 and 12 years. Unbound ropivacaine hydrochloride and PPX clearance and ropivacaine hydrochloride 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 hydrochloride clearance appears to be complete by the age of 3 years, that of PPX by the age of 1 year and unbound ropivacaine hydrochloride 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 hydrochloride clearance (Clu) for ages above 6 months has reached values within the range of those in adults. Total ropivacaine hydrochloride clearance (Cl) values displayed in the table are those not affected by the postoperative increase in AAG.

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

Age	BW[a]	Clu[b]	Vu[c]	Cl[d]	$t_{1/2}$[e]	$t_{1/2ppx}$[f]
Group	kg	(l/h/kg)	(l/kg)	(l/h/kg)	(h)	(h)
Newborn	3.27	2.40	21.86	0.096	6.3	43.3
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 hydrochloride clearance
[c] Ropivacaine hydrochloride unbound volume of distribution
[d] Total ropivacaine hydrochloride clearance
[e] Ropivacaine hydrochloride 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. 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 section 4.4).

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

Age group	Dose	Cu_{max} [a]	t_{max} [b]	Cu_{max} [c]
	(mg/kg)	(mg/l)	(h)	(mg/l)
0-1 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 hydrochloride clearance has reached 34% and unbound PPX 71% of its mature value. The systemic exposure is higher in neonates and also somewhat higher in infants between 1 to 6 months compared to older infants and 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 hydrochloride and PPX, based on the PK parameters and their variance in the population analysis, indicate that for a single caudal block the recommended dose must be increased by a factor of 2.7 in the youngest group and a factor of 7.4 in the 1 to 10 year group in order for the upper prediction 90% confidence interval limit to touch the threshold for systemic toxicity. Corresponding factors for the continuous epidural infusion are 1.8 and 3.8, respectively.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
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 hydrochloride shows poor solubility at pH > 6.0.

6.3 Shelf life

Shelf-life before opening
3 years

Shelf-life after opening

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

6.4 Special precautions for storage

Do not freeze.
For storage conditions after opening the medicinal product, see section 6.3.

6.5 Nature and contents of container

Ropivacaine 2 mg/ml solution for injection:
Polypropylene ampoules:
10 x 10ml, 10 x 20ml - sterile ampoule, in plastic overwrap

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

6.6 Special precautions for disposal and other handling

Handling
Ropivacaine products are preservative free and 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 product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals Ltd
Capital House
85 King William Street
London EC4N 7BL
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0899/041/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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