SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ropivacaine B. Braun 7.5 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 7.5 mg ropivacaine hydrochloride (as ropivacaine hydrochloride monohydrate).

1 ampoule of 10 ml or 20 ml solution for injection contains 75 mg or 150 mg ropivacaine hydrochloride as ropivacaine hydrochloride monohydrate.

Excipients with known effect:

Ropivacaine B. Braun 7.5 mg/ml solution for injection contains 2.9 mg/ml 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 – 6 and an osmolality of 270 – 320 mOsmol/kg

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

The medicinal product is indicated in adults and children above 12 years for:

Surgical anaesthesia:

- Epidural blocks for surgery, including Caesarean section
- Major nerve blocks
- Field blocks

4.2. Posology and method of administration

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

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

Posology

Adults and adolescents above 12 years of age

The following table is a guide to dosage for the more commonly used blocks in the average adult. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements. 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 on the dose.

	Concentration of ropivacaine hydrochloride	**Volume**	**Dose of ropivacaine hydrochloride**	**Onset**	**Duration**
	mg/ml	**ml**	**mg**	**minutes**	**hours**
SURGICAL ANAESTHESIA					
Lumbar Epidural Administration					
Surgery	7.5	15-25	113-188	10-20	3-5
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 (depending 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.

(1) A starting dose of approximately 100 mg (13 ml - 14 ml) of ropivacaine hydrochloride should be given over 3–5 minutes. Two extra doses, in total additional 50 mg, 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 adversereactions, regardless of the local anaesthetic used, (see section 4.4 Special warnings and precautions for use).

* 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.

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

The use of concentrations above 7.5 mg/ml ropivacaine hydrochloride has not been documented for Caesarean section.

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 of 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 of up to 28 mg/hour ropivacaine hydrochloride 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 a concentration of 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.

Combination with opioids:

In clinical studies an epidural infusion of 2 mg/ml ropivacaine hydrochloride 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 undesirable effects. The combination of ropivacaine 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 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.

Paediatric population

The use of Ropivacaine 7.5 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 to this population.

Renal impairment

Dose modification is not normally required in patients with impaired renal function when single doses or short-term treatments are used (see section 4.4 and 5.2).

Hepatic impairment

Ropivacaine hydrochloride is metabolized in the liver and should be used with caution in patients with severe liver disease. Reduced repeat doses may be required due to delayed elimination (see section 4.4 and 5.2).

Method of administration

For perineural and epidural use.

Careful aspiration before and during injection is recommended to prevent intravascular injection. When a large dose is to be injected, a test dose of lidocaine 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.

Ropivacaine hydrochloride 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.

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

4.3. Contraindications

- Hypersensitivity to ropivacaine, to other local anaesthetics of the amide type or to any of the excipients listed in section 6.1
- Intravenous regional anaesthesia (Bier's block)
- Obstetric paracervical anaesthesia
- Hypovolaemia

General contraindications related to regional anaesthesia, including neuraxial anaesthesia, should be taken into account.

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 responsible clinician should take the necessary precautions to avoid intravascular injection (see section 4.2) and be appropriately trained and familiar with diagnosis and treatment of side effects, systemic toxicity

and other complications (see section 4.8 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 risk

Epidural (and accidental administered intrathecal) anaesthesia may lead to hypotension and bradycardia. Hypotension should be treated promptly with a vasopressor intravenously, and with adequate vascular filling. Patients treated with anti-arrhythmic agents class III (e.g. amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive. There have been rare reports of cardiac arrest during the use of 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.

Hypovolaemia

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

Patients in poor general health

Patients in poor general condition due to advanced age 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 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 textbooks 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. The majority of reported cases of chondrolysis have involved the shoulder joint. Intra-articular continuous infusion is not an approved indication for Ropivacaine B. Braun. Intra-articular continuous infusion with Ropivacaine B. Braun should be avoided, as the efficacy and safety has not been established.

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).

Special warnings/precautions regarding excipients

This medicinal product contains 2.9 mg sodium per ml, equivalent to 0.1 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric population

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. 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, SpO2) 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 7.5 mg/ml in children up to and including 12 years has not been established.

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 hydrochloride with general anaesthetics or opioids may potentiate each others' (adverse) effects. Specific interaction studies with ropivacaine and anti-arrhythmic agents 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 coadministration of fluvoxamine, a

selective and potent CYP1A2 inhibitor. Prolonged administration of ropivacaine should be avoided in patients concomitantly treated with strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin as they can interact with ropivacaine hydrochloride. (see section 4.4).

In vivo the plasma clearance of ropivacaine was reduced by 15% during coadministration with 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 ropivacaine in human pregnancy. Experimental animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Lactation

There is insufficient information on the excretion of ropivacaine into human milk.

Fertility

No data available

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 co-ordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and reactivity. When administered this medicine the doctor should assess on each particular case if the reaction capacity is engaged and if the patient can drive or use machinery.

4.8 Undesirable effects

The adverse reaction profile for ropivacaine hydrochloride is similar to those for other long acting local anaesthetics of the amide type.

Adverse reactions should be distinguished from the physiological effects of the nerve block itself e.g. a hypotension and bradycardia during spinal/epidural block.

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

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 drug or the type of block.

Table of adverse reactions

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)

Within each system organ class, the adverse reactions have been ranked under the headings of frequency, most frequent reactions first.

Immune system disorders	*Rare*
	Allergic reactions (urticaria, angioneurotic oedema and anaphylactic reaction)
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, muscle twitching, dysarthria, tremor, hypoaesthesia)*
	Not known
	Dyskinesia
Cardiac disorders	*Common*
	bradycardia, tachycardia
	Rare
	cardiac arrest, arrhythmias
Vascular disorders	*Very common*
	hypotension
	Common
	hypotension (children), hypertension
	Uncommon

	syncope
Respiratory, thoracic and mediastinal disorders	*Uncommon* dyspnoea
Gastrointestinal disorders	*Very common* nausea, vomiting (children) *Common* vomiting
Musculoskeletal and connective tissue disorders	*Common* rigidity, back pain
Renal and urinary disorders	*Common* urinary retention
General disorders and administration site conditions	*Common* temperature elevation, chills *Uncommon* hypothermia

* These symptoms usually occur because of inadvertent intravascular injection, overdose or rapid absorption (see section 4.9).

Class-related adverse reactions

Neurological complications

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

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)

4.9 Overdose

Symptoms

Acute systemic toxicity

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

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, lightheadedness, tingling and paraesthesia are seen. Dysarthria, muscular rigidity and tremor 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 hypercapnia 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 prolongs 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 may be rapid unless large amounts of the drug 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 resulted in signs of depression of conductivity and contractility.

Cardiovascular toxicity 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.

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

Treatment

Equipment and medicinal products necessary for monitoring and emergency resuscitation should be immediately available.

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 medicinal products. 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 Anaesthetics; 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, see section 4.2.
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 this drug indicates a good margin of safety when adequately used in recommended doses.

5.2 Pharmacokinetic properties

Ropivacaine 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 ropivacaine.
<u>Absorption</u>
The plasma concentration of ropivacaine depends upon the dose, the route of administration and the vascularity of the injection site. Ropivacaine, when administered iv, 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 children.

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.

Distribution

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

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 and the 4-hydroxy-dealkylated accounts for 1 - 3%. Conjugated and unconjugated 3-hydroxy-ropivacaine shows only detectable concentrations in plasma.

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

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.

There is no evidence of in vivo racemisation of ropivacaine.

Paediatric population

The pharmacokinetics of ropivacaine was characterized 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 below are those not affected by the postoperative increase in AAG.

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
1m	4.29	3.60	25.94	0.143	5.0	25.7
6m	7.85	8.03	41.71	0.320	3.6	14.5
1y	10.15	11.32	52.60	0.451	3.2	13.6
4y	16.69	15.91	65.24	0.633	2.8	15.1
10y	32.19	13.94	65.57	0.555	3.3	17.8

[a] Median bodyweight for respective age taken 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 (Cumax) after a single caudal block tended to be higher in neonates and the time to Cumax (tmax) 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 also section 4.4).

Simulated mean and observed range of unbound Cumax after a single caudal block

Age group	Dose (mg/kg)	Cumax[a] (mg/l)	tmax[b] (h)	Cumax[c] (mg/l)
0-1m	2.00	0.0582	2.00	0.05-0.08 (n=5)
1-6m	2.00	0.0375	1.50	0.02-0.09 (n=18)
6-12m	2.00	0.0283	1.00	0.01-0.05 (n=9)
1-10y	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 1–10 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 is0.053 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development, 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 0.36% (for pH adjustment)

Sodium hydroxide 0.4% (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.

6.3 Shelf life

- unopened:

3 years for LDPE ampoules

- Shelf life after first opening:

After opening the product must be used immediately.

– after dilution or mixture with additives

Not applicable

6.4 Special precautions for storage

Do not freeze.

Do not store above 30°C

6.5 Nature and contents of container

10 ml and 20 ml polyethylene (LDPE) ampoules in packs of 20

The LDPE ampoules are specially designed to fit Luer lock and Luer fit syringes. Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

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

For single use. Discard container and any unused content after use.

Inspect the medicinal product visually before use.

Only to be used if solution is clear and colourless and the containers are undamaged.

7. MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:

B. Braun Melsungen AG

34209 Melsungen, Germany

Manufactured by:

B. Braun Melsungen AG

Mistelweg 2, 12357 Berlin, Germany

Imported by: B. Braun (Thailand) Ltd., Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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