SCHEDULING STATUS

S4

1. Name of the Medicinal Product

Ropivacaine 2 mg/mL B.Braun solution for injection/infusion

Ropivacaine 5 mg/mL B.Braun solution for injection

Ropivacaine 7,5 mg/mL B.Braun solution for injection

Ropivacaine 10 mg/mL B.Braun solution for injection

2. Qualitative and Quantitative Composition

Ropivacaine 2 mg/mL B. Braun solution for injection/infusion:

1 mL solution for injection/infusion contains 2 mg ropivacaine hydrochloride (as ropivacaine hydrochloride monohydrate).

1 ampoule of 10 mL or 20 mL solution for injection/infusion contains 20 mg or 40 mg ropivacaine hydrochloride as ropivacaine hydrochloride monohydrate.

1 bottle of 100 mL, 200 mL, 400 mL, or 500 mL solution for injection/infusion contains 200 mg, 400 mg, 800 mg or 1000 mg ropivacaine hydrochloride as ropivacaine hydrochloride monohydrate.

Excipients with known effect: 3.3 mg/mL sodium

Ropivacaine 5 mg/mL B. Braun solution for injection:

1 ml solution for injection contains 5 mg ropivacaine hydrochloride (as ropivacaine hydrochloride monohydrate).

1 ampoule of 10 mL or 20 mL solution for injection contains 50 mg or 100 mg ropivacaine hydrochloride as ropivacaine hydrochloride.

Excipients with known effect: 3.1 mg/mL sodium.

Ropivacaine 7.5 mg/mL B. Braun solution for injection:

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: 2.9 mg/mL sodium.

Ropivacaine 10 mg/mL B. Braun solution for injection:

1 mL solution for injection contains 10 mg ropivacaine hydrochloride (as ropivacaine hydrochloride monohydrate).

1 ampoule of 10 mL or 20 mL solution for injection contains 100 mg or 200 mg ropivacaine hydrochloride as ropivacaine hydrochloride monohydrate.

Excipients with known effect: 2.7 mg/mL sodium.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Solution for injection/infusion

Clear, colourless solution with a pH of 4 – 6 and an osmolality of 270 – 320 mOsmol/kg

4. Clinical Particulars :

4.1. Therapeutic indications

Adults: 2 mg/mL, 7,5 mg/mL, 10 mg/mL.

Surgical anaesthesia:

Epidural block for surgery, including Caesarean section

Minor nerve block and infiltration anaesthesia

Major nerve block

Acute pain management:

- Continuous epidural infusion or intermittent bolus administration e.g. postoperative or labour pain.
- Minor nerve block and infiltration analgesia.
- Continuous peripheral nerve block infusion or intermittent injections, e.g. postoperative pain management.

Children (1 to 12 years of age): 2 mg/mL and 5 mg/mL.

Acute pain management in paediatrics:

- Caudal epidural block
- Peripheral nerve block for per and postoperative pain management.

4.2 Posology and method of administration

ROPIVACAINE B BRAUN should only be used by or under the supervision of clinicians experienced in regional anaesthesia. **ROPIVACAINE B BRAUN** should not be administered intravenously.

In order to avoid intravascular injection, aspiration should be repeated prior to and during administration of the main dose, which should be injected slowly or in incremental doses, at a rate of 25 to 50 mg/min, while closely observing the patient's vital functions and maintaining

verbal contact. When an epidural dose is to be injected, a standard test dose technique is advised. 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. If toxic symptoms occur, the injection should be stopped immediately.

Adults and children above 12 years of age:

The following table is a guide to dosage for the more commonly used blocks. The clinician's experience and knowledge of the patient's physical status are of importance when deciding the dose. In general, surgical anaesthesia (e.g. epidural administration) requires the use of the higher concentrations and doses.

For analgesia the 2 mg/mL concentration is generally recommended.

ROPIVACAINE B BRAUN is not recommended for children under the age of 1 year and in patients under 60 kg for major nerve block anaesthesia, as safety and efficacy have not been established.

Dosage recommendations for ROPIVACAINE B BRAUN in adults:

	Conc. mg/mL	Volume mL	Dose mg	Onset minutes	Duration hours
SURGICAL ANAESTHESIA					
Lumbar Epidural					
Surgery	7,5	15 to 25	113 to 188	10 to 20	3 to 5
	10,0	15 to 20	150 to 200	10 to 20	4 to 6
Lumbar Epidural					

Caesarean Section	7,5	15 to 20	113 to 150	10 to 20	3 to 5
Thoracic Epidural Administration					
To establish block for postoperative pain relief	7,5	5 to 15 Depending on level of injection	38 to 113	10 to 20	n/a
Minor Nerve Block and infiltration					
(e.g. minor nerve blocks and infiltration)	7,5	1 to 30	7,5 to 225	1 to 15	2 to 6
Major Nerve Block					
(e.g. brachial plexus)	7,5	10 to 40	75 to 300*	10 to 25	6 to 10
ACUTE PAIN MANAGEMENT					
Lumbar Epidural					
Bolus	2,0	10 to 20	20 to 40	10 to 15	0,5 to 1,5
Intermittent injections (top-up) (e.g. labour pain management)	2,0	10 to 15 (minimum interval 30 minutes)	20 to 30		
Lumbar Epidural Administration					
Continuous infusion	2,0	6 to 10 mL/h	12 to 20 mg/h	n/a	n/a
(e.g. Labour pain Postoperative pain	2,0	6 to 14 mL/h	12 to 28 mg/h	n/a	n/a
ACUTE PAIN MANAGEMENT					
Thoracic Epidural Administration					

Continuous infusion (e.g. postoperative pain management)	2,0	6 to 14 mL/h	12 to 28 mg/h	n/a	n/a
Minor Nerve Block and infiltration analgesia					
(e.g. minor nerve blocks and infiltration)	2,0	1 to 100	2 to 200	1 to 5	2 to 6
Peripheral Nerve Block					
Femoral or interscalene block Continuous infusion or intermittent injections (e.g. postoperative pain management)	2,0	5 to 10 mg/h	10 to 20 mg/h	n/a	n/a

*ROPIVACAINE B BRAUN plasma concentrations may approach the threshold for central nervous toxicity after administration of 300 mg of ropivacaine for brachial plexus block in adult patients of 60 kg or more. Data on patients under 60 kg is not available. Caution should be exercised when using the 300 mg dose.

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.

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 reflect the expected average dose range needed. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements. When prolonged epidural 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 800 mg ROPIVACAINE B BRAUN 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.

For treatment of postoperative pain, the following technique can be recommended: Unless preoperatively instituted, an epidural block with ROPIVACAINE 7,5 mg/mL B.BRAUN is induced via an epidural catheter (preoperatively placed). Analgesia is maintained with ROPIVACAINE 2 mg/mL B.BRAUN infusion.

Clinical studies have demonstrated that infusion rates of 6 to 14 mL (12 mg to 28 mg) per hour provide adequate analgesia with only slight and non-progressive motor block in most cases of moderate to severe postoperative pain.
For caesarean section, neither intrathecal administration nor the use of the ROPIVACAINE B BRAUN concentration 10 mg/mL for epidural administration, have been documented.

Pediatrics:

Dosage recommendations for pediatric patients 1 to 12 years of age:

ACUTE PAIN MANAGEMENT (peri- and postoperative)	Conc. mg/m	Volume mL/kg	Dose mg/kg
Single caudal epidural block administration Blocks below T12, in children with a body weight up to 25 kg	2,0	1	2
Peripheral nerve block (e.g. ilioinguinal nerve block)	5,0	0,6	3

The doses in the table should be regarded as guidelines for use in paediatrics. Individual variations occur. In children with a high body weight a gradual reduction of the dosage is often necessary and should be based on the ideal body weight. The volume for single caudal epidural block 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 single caudal epidural injection of ropivacaine 2 mg/mL produces adequate postoperative analgesia below T12 in the majority of patients when a dose of 2 mg/kg is used in a volume of 1 mL/kg. In children above 4 years of age, doses up to 3 mg/kg have been studied.
However, this concentration is associated with a higher incidence of motor block. The volume of the caudal epidural injection may be adjusted to achieve a different distribution of sensory block, as recommended in standard textbooks.

For ilioinguinal block, a single injection of ropivacaine 5 mg/mL produces effective analgesia when a dose of 3 mg/kg in a volume of 0,6 mL/kg is used.

Fractionation of the calculated local anaesthetic dose is recommended, whatever the route of administration.
Until further experience has been gained, ROPIVACAINE B BRAUN cannot be recommended for use in children below the age of 1 year. Concentrations above 5 mg/mL have not been documented for children.

NOTE:

The products contain no preservatives and are intended for single use only. Any solution remaining from an opened container should be discarded.

Alkalisation may lead to precipitation since ropivacaine is poorly soluble above pH 6,0.

ROPIVACAINE B BRAUN solution for infusion in plastic infusion bags is chemically and physically compatible with the following medicines:

Concentration of ROPIVACAINE B BRAUN: 1 to 2 mg/mL	
Additive	Concentration
Fentanyl citrate	1,0 to 10,0 microgram/mL
Sufentanil citrate	0,4 to 4,0 microgram/mL
Morphine sulphate	20,0 to 100,0 microgram/mL
Clonidine hydrochloride	5,0 to 50,0 microgram/mL

The mixtures are chemically and physically stable for 30 days at up to 30 °C. From a microbiological point of view, the mixtures should be used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Method of administration

For perineural and epidural use.

Careful aspiration before and during injection or infusion is recommended to prevent intravascular injection.

The patient's vital functions should be observed closely during the injection or infusion. If toxic symptoms occur, the injection or infusion should be stopped immediately.

4.3. Contraindications

- ROPIVACAINE B BRAUN solutions are contraindicated in patients with known hypersensitivity to ropivacaine, to other local anaesthetics of the amide-type or to any excipients listed in section 6.1.

- Intravenous regional anaesthesia (Bier's block). Obstetric paracervical anaesthesia.

- Local anaesthetics are contraindicated for epidural and spinal anaesthesia in patients with uncorrected hypotension.

Local anaesthetic techniques must not be used when there is inflammation and/or sepsis in the region of the proposed injection and/or in the presence of septicaemia.

General contraindications related to epidural anaesthesia, regardless of the local anaesthetic used should be taken into account.

Until further experience has been documented ROPIVACAINE B BRAUN is not recommended in children under the age of 1 year.

ROPIVACAINE 7,5 mg/mL and 10 mg/mL B. BRAUN should not be used in children below the age of 12 years as safety and efficacy have not been established.

4.4. Special warnings and precautions for use

Safe use of ROPIVACAINE B BRAUN in lactating or pregnant women, other than those in labour has not been established (see section 4.6) Regional anaesthetic procedures should always be performed in a properly equipped and staffed area. Resuscitative equipment and medicinal products necessary for monitoring and emergency resuscitation, including oxygen

should be immediately available in order to manage possible adverse reactions involving cardiovascular, respiratory or central nervous systems.

Patients receiving major blocks should be in an optimal and haemodynamically stable condition and have an intravenous line inserted before the blocking procedure because of the possibility of hypotension and bradycardia following major blocks. Injection should always be made slowly with frequent aspirations to avoid inadvertent intravascular injection, which can produce toxic effects.

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. And also after intrathecal administration, systemic toxicity is not expected to occur, due to the low dose administered. An excessive dose administered into the subarachnoid space may give rise to a total spinal block (see section 4.9).

ROPIVACAINE B BRAUN should not be given to patients with pre-existing abnormal neurological pathology, e.g. myasthenia gravis. Epidural, caudal and spinal anaesthesia should not be used in serious diseases of the CNS or of the spinal cord, e.g. meningitis, spinal fluid block, cranial or spinal haemorrhage, tumours, poliomyelitis, syphilis, tuberculosis or metastatic lesions of the spinal cord.

Caution is required to prevent injections in inflamed areas.

LOW MOLECULAR WEIGHT HEPARINS AND HEPARINOIDS (Spinal/Epidural Haematomas) - When neuraxial anaesthesia (epidural/spinal anaesthesia) is employed, patients anti-coagulated or scheduled to be anti-coagulated with low molecular weight heparins or heparinoids are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters, traumatic or repeated epidural/spinal puncture, and the concomitant use of medicines affecting haemostasis such as NSAIDs, platelet inhibitors or other anticoagulants. Patients should be frequently monitored for signs and symptoms of neurological impairment.

The safety and efficacy of ROPIVACAINE B BRAUN depends on proper dosage, correct technique and adequate precautions. Standard textbooks should be consulted regarding specific techniques and precautions for various regional anaesthetic procedures.

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

Cardiovascular risk

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.

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 HCl B. Braun 2 mg/mL** solution for injection/infusion. Intra-articular continuous infusion with **Ropivacaine HCl B. Braun 2 mg/mL** solution for injection/infusion 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

Ropivacaine 2 mg/mL B.Braun : This medicinal product contains 3.3 mg sodium per mL, equivalent to 0.2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Ropivacaine 5 mg/mL B.Braun: This medicinal product contains 3.1 mg sodium per mL, equivalent to 0.2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Ropivacaine 7.5 mg/mL B.Braun : 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, 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, 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 **ROPIVACINE B BRAUN** has not been established for infants < 1 year.

The safety and efficacy of **ROPIVACINE 7,5 mg/mL and 10 mg/mL B. BRAUN** has not been established for children ≤12 years.

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 other's' (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 significantly during coadministration of fluvoxamine, a selective and potent CYP1A2 inhibitor. Prolonged administration of ropivacaine should be avoided in patients concomitantly treated with strong CYP1A2 inhibitors, 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 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.

Foetal bradycardia frequently follows paracervical block with some amide-type local anaesthetics (such as **ROPIVACAINE B BRAUN**) and may be associated with foetal acidosis. Added risk appears to be present in prematurity, toxaemia of pregnancy and foetal distress. Until further clinical experience in pregnancy is gained, the use of **ROPIVACAINE B BRAUN** is not recommended.

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. However, 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, for instance, the occurrence of dizziness, or headache may influence the ability to drive and 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.

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

System organ class	
Immune system disorders	*Less frequent* allergic reactions (urticaria, angioneurotic oedema and anaphylactic reaction up to anaphylactic shock)

Psychiatric disorders	*Less frequent* anxiety
Nervous system disorders	*Frequent* paraesthesia, dizziness, headache *Less frequent* 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)* *Less frequent* HORNER's syndrome** *Frequency not known* Dyskinesia
Cardiac disorders	*Frequent* bradycardia, tachycardia *Less frequent* cardiac arrest, arrhythmias
Vascular disorders	*Frequent* hypotension, hypotension (children), hypertension *Less frequent* syncope
Respiratory, thoracic and mediastinal disorders	*Less frequent* dyspnoea
Gastrointestinal disorders	*Frequent* nausea, vomiting (children), vomiting
Musculoskeletal and connective tissue disorders	*Frequent* back pain
Renal and urinary disorders	*Frequent* urinary retention
General disorders and administration site conditions	*Frequent* temperature elevation, chills *Less frequent* hypothermia

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

** Associated with epidural anaesthesia or regional applications in the head/neck region.

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 and vomiting which happens more often in children.

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).

Reporting of suspected adverse reactions

Reporting suspected adverse reaction after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://sahpra.org.za/Publications/Index/8

4.9 Overdose

Accidental intravascular injections of **ROPIVACAINE B BRAUN** may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, systemic toxicity appears later (15 to 60 minutes after injection) due to the slower increase in local anaesthetic blood concentration.

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 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.

Early signs of local anaesthetic toxicity may be difficult to detect if the block is performed during general anaesthesia.

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 is 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 and possible loss of functional airways. 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.

Hypotension, bradycardia, dysrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics, but in rare cases cardiac arrest has occurred without prodromal CNS effects. In children, early signs of local anaesthetic toxicity may be difficult to detect since they may not be able to verbally express them, or if they are under general anaesthesia.

Treatment of acute systemic toxicity

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 A.4 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 is 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.

Absorption

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 up to 80 mg.

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.

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 α_1-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 barely 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.

Special populations

Elderly

Ropivacaine plasma clearance is reduced and the elimination half-life prolonged in this population. Therefore when injected continuously, the dose should be individualized (eventually decreased) to avoid accumulation of ropivacaine.

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 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)**
New-born	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 (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 also section 4.4).

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)**
0-1m	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.

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

Ropivacaine 2 mg/mL B.Braun: This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Ropivacaine 5 mg/mL, 7,5 mg/mL and 10 mg/mL B.Braun:

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Ropivacaine 2 mg/mL B.Braun :

- *unopened:*

30 months for LDPE ampoules

3 years for LDPE bottles

- *after first opening the container:*

After first opening the product must be used immediately.

– *after dilution or mixture with additives:*

Chemical and physical stability of mixtures with the solutions listed in section 6.6 has been demonstrated for 30 days at 30 °C.

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.

Ropivacaine 5 mg/mL, 7,5 mg/mL and 10 mg/mL B.Braun:

– *unopened:*

30 months for LDPE ampoules

- *Shelf life after first opening:*

After first opening the product must be used immediately.

– *after dilution or mixture with additives:*

Not applicable

6.4 Special precautions for storage

Store at or below 30 °C. Do not freeze.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Ropivacaine 2 mg/mL, 5 mg/mL, 7,5 mg/mL and 10 mg/mL B.Braun:

LDPE ampoules: 10 mL and 20 mL in packs of 20.

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

Ropivacaine 2 mg/ ml B.Braun:

LDPE bottles: Contents 100 mL, 200 mL, 400 mL and 500 mL in packs of 1 and 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal 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 container and its closure are undamaged.

Ropivacaine B. Braun is chemically and physically compatible with the following active substances:

Concentration of Ropivacaine: 1–2 mg/mL	
Additive	Concentration
Fentanyl citrate	1-10 microgram/mL
Morphine sulfate	20-100 microgram/mL
Sufentanil citrate	0.4-4 microgram/mL

7 HOLDER OF THE CERTIFICATE OF REGISTRATION:

B. Braun Medical (Pty) Ltd,

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South Africa 2194.

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8. REGISTRATION NUMBER:

Ropivacaine 2mg/mL: 48/4/0349

Ropivacaine 5mg/mL: 48/4/0350

Ropivacaine 7,5mg/mL: 48/4/0351

Ropivacaine 10mg/mL: 48/4/0352

9: DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION:

25 January 2022