APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

- **ROPIVACAINE 2 mg/ml INJECTION FRESENIUS** Solution for injection
- **ROPIVACAINE 2mg/ml INFUSION FRESENIUS** Solution for infusion
- **ROPIVACAINE 5 mg/ml INJECTION FRESENIUS** Solution for injection
- **ROPIVACAINE 7,5 mg/ml INJECTION FRESENIUS** Solution for injection
- **ROPIVACAINE 10 mg/ml INJECTION FRESENIUS** Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

- **ROPIVACAINE 2 mg/ml INJECTION FRESENIUS:**

1 ml of solution for injection contains ropivacaine hydrochloride equivalent to 2 mg ropivacaine hydrochloride:

1 ampoule of 10 ml solution for injection contains 20 mg ropivacaine hydrochloride.

1 ampoule of 20 ml solution for injection contains 40 mg ropivacaine hydrochloride.

- **ROPIVACAINE 2 mg/ml INFUSION FRESENIUS:**

1 ml of solution for infusion contains ropivacaine hydrochloride equivalent to 2 mg ropivacaine hydrochloride:

Each 100 ml bag contains 200 mg ropivacaine hydrochloride.

Each 200 ml bag contains 400 mg ropivacaine hydrochloride.

- **ROPIVACAINE 5 mg/ml INJECTION FRESENIUS:**

1 ml of solution contains ropivacaine hydrochloride equivalent to 5 mg ropivacaine hydrochloride:

1 ampoule of 10 ml solution for injection contains 50 mg ropivacaine hydrochloride.

- **ROPIVACAINE 7,5 mg/ml INJECTION FRESENIUS:**

1 ml of solution contains ropivacaine hydrochloride equivalent to 7,5 mg ropivacaine hydrochloride:

Each ampoule of 10 ml solution for injection contains 75 mg ropivacaine hydrochloride.

Each ampoule of 20 ml solution for injection contains 150 mg ropivacaine hydrochloride.

- **ROPIVACAINE 10 mg/ml INJECTION FRESENIUS:**

1 ml of solution contains ropivacaine hydrochloride equivalent to 10 mg ropivacaine hydrochloride:

Each ampoule of 10 ml solution for injection contains 100 mg ropivacaine hydrochloride.

Each ampoule of 20 ml solution for injection contains 200 mg ropivacaine hydrochloride.

Excipient with known effect:

Ropivacaine 2 mg/ml Solution Fresenius:
Each 10 ml ampoule contains 1,48 mmol (or 34 mg) sodium.
Each 20 ml ampoule contains 2,96 mmol (or 68 mg) sodium.

Ropivacaine 2 mg/ml Infusion Fresenius:
Each 100 ml bag contains 14,8 mmol (or 340 mg) sodium.
Each 200 ml bag contains 29,6 mmol (or 680 mg) sodium.
Ropivacaine 5 mg/ml Solution Fresenius:
Each 10 ml ampoule contains 1,38 mmol (or 31,7 mg) sodium.
Each 20 ml ampoule contains 2,76 mmol (or 63,4 mg) sodium.
Ropivacaine 7,5 mg/ml Solution Fresenius:
Each 10 ml ampoule contains 1,3 mmol (or 29,9 mg) sodium.
Each 20 ml ampoule contains 2,6 mmol (or 59,8 mg) sodium.
Ropivacaine 10 mg/ml Solution Fresenius:
Each 10 ml ampoule contains 1,2 mmol (or 28 mg) sodium.
Each 20 ml ampoule contains 2,4 mmol (or 56 mg) sodium.

Sugar-free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.

Clear, colourless solution with a pH of 4,0 to 6,0 and an osmolality between 255 and 305 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Indications

ROPIVACAINE FRESENIUS is indicated for:

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 - 12 years of age): 2 mg/ml and 5 mg/ml

Acute pain management in paediatrics:

- Caudal epidural block;
- Peripheral nerve block;

for pre- and postoperative pain management.

4.2 Posology and method of administration

ROPIVACAINE FRESENIUS should only be used by or under the supervision of a medical practitioner experienced in regional anaesthesia.

Posology

ROPIVACAINE FRESENIUS should not be administered intravenously (see "Method of administration").

Adults and children above 12 years of age:

The table below is a guide to dosage for the more commonly used blocks. The medical practitioner'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 FRESENIUS 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 in adults:

PROCEDURE	Conc. mg/**ml**	Volume **ml**	Dose mg	Onset minutes	Duration hours
SURGICAL ANAESTHESIA					
Lumbar epidural administration:					
Surgery	7,5	15 to 25	113 to 188	10 - 20	3 to 5
	10,0	15 to 20	150 to 200	10 - 20	4 to 6
Lumbar epidural administration:					
Caesarean section	7,5	15 to 20	113 to 150	10 - 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 anaesthesia:					
(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 administration:					
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 min.)	20 to 30		
Lumbar epidural administration					
Continuous infusion (e.g. labour pain)	2,0	6 to 10 ml/h	12 to 20 mg/ h	n/a	n/a
Postoperative pain management	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 mg/ h	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	5-10 ml/h	10-20 mg/ h	n/a	n/a

* ROPIVACAINE FRESENIUS plasma concentrations may approach the threshold for central nervous system (CNS) toxicity after administering doses of 300 mg for a brachial plexus block in adult patients of 60 kg or more. Data on patients under 60 kg are not available. Exercise caution when using the 300 mg dose.

Adjust the dose for a major nerve block 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.

When using prolonged epidural blocks, either through continuous infusion or through repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing local neural injury should be considered.

Cumulative doses of up to 800 mg ROPIVACAINE FRESENIUS 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 INJECTION FRESENIUS is induced via an epidural catheter (preoperatively placed). Analgesia is maintained with ROPIVACAINE 2mg/ml INFUSION FRESENIUS.

It has been demonstrated that infusion rates of 6 to 14 ml (12 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 FRESENIUS concentration 10 mg/ml for epidural administration, has been documented.

Paediatric patients 1 to 12 years of age:

Dosage recommendations for paediatric patients 1-12 years of age:

ACUTE PAIN MANAGEMENT (pre- and postoperative)	**Conc.** **mg/ml**	**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. Consult standard textbooks for factors affecting specific block techniques and for individual patient requirements.

A single caudal epidural injection of ROPIVACAINE 2 mg/ml INJECTION FRESENIUS produces adequate postoperative analgesia below T12 in most 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 of a concentration of ropivacaine 3 mg/ml have been used. 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 INJECTION FRESENIUS 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, irrespective of the route of administration.

ROPIVACAINE FRESENIUS is not recommended for children under the age of 1 year. Concentrations above 5 mg/ml have not been documented for children.

Method of administration

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

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 - 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. Inadvertent intravascular injection may be recognised by a temporary increase in heartrate and an accidental intrathecal injection by signs of a spinal block. If toxic symptoms occur, the injection should be stopped immediately.

The products contain no preservatives and are intended for single use only. See section 6 for information on handling of the injection/infusion and for compatibility of the infusion with other medicines.

ROPIVACAINE 2 mg/ml INFUSION FRESENIUS solution for infusion in plastic infusion bags is chemically and physically compatible with the following medicines:

Concentration of ROPIVACAINE FRESENIUS: 1 to 2 mg/ml	
Additive	**Concentration***
Fentanyl citrate	1,0 – 10,0 µg/ml
Sufentanil citrate	0,4 – 4,0 µg/ml
Morphine sulphate	20,0 – 100,0 µg/ml
Clonidine hydrochloride	5,0 – 50 µg/ml

Chemical and physical stability of these mixtures have been demonstrated 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.

4.3 Contraindications

ROPIVACAINE FRESENIUS is contraindicated in:

- patients with known hypersensitivity to ropivacaine or any excipient of ROPIVACAINE FRESENIUS (see section 6.1);
- patients with known hypersensitivity to other amide-type local anaesthetics;
- intravenous regional anaesthesia (Bier's block) (see section 4.4)
- obstetric paracervical anaesthesia;
- epidural and spinal anaesthesia in patients with uncorrected hypotension;
- patients with hypovolaemia;
- patients with inflammation and/or sepsis in the region of the proposed injection and/or the presence of septicaemia.

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

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

ROPIVACAINE FRESENIUS 7,5 mg/ml and 10 mg/ml 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 FRESENIUS in lactating or pregnant women, other than by those in labour, has not been established.

Do not use ROPIVACAINE FRESENIUS for major nerve blocks unless the patients are in an optimal and haemodynamically stable condition.

Regional anaesthetic procedures with ROPIVACAINE FRESENIUS should always be performed in a properly equipped and staffed area. Equipment and medicines necessary for monitoring and emergency resuscitation should be available immediately. Patients receiving major blocks should be in an optimal condition and have an IV line inserted before the blocking procedure.

When any local anaesthetic substance is used, resuscitative equipment and medicines, including oxygen, should be immediately available to manage possible adverse reactions involving the cardiovascular, respiratory or central nervous systems. Because of the possibility of hypotension and bradycardia following major blocks, an IV cannula should be inserted before the local anaesthetic is injected. Always inject slowly with frequent aspirations to avoid inadvertent intravascular injection, which can produce toxic effects.

The medical practitioner 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 side effects, systemic toxicity and other complications (see sections 4.8 and 4.9) such as inadvertent subarachnoid injection which may produce a high spinal block with apnoea and hypotension.

ROPIVACAINE FRESENIUS should be administered in incremental doses, since ROPIVACAINE FRESENIUS should not be injected rapidly in large doses. It is not

recommended for emergency situations, where a fast onset of surgical anaesthesia is necessary.

Local anaesthetics should only be employed by medical practitioners who are well versed in the diagnosis and management of dose related toxicity and other acute emergencies which might arise from the block to be employed, then only after ensuring the immediate (without delay) availability of oxygen, other resuscitative medicines, cardiopulmonary resuscitative equipment, and the staff resources needed for proper management of toxic reactions and related emergencies. Delay in proper management of dose related toxicity, under-ventilation from any cause and/or altered sensitivity may lead to the development of acidosis, cardiac arrest and possibly, death.

Solutions of ROPIVACAINE FRESENIUS should not be used for the production of obstetrical paracervical block anaesthesia, retrobulbar block, or spinal anaesthesia (subarachnoid block) due to insufficient data to support such use.

Intravenous regional anaesthesia (Bier block) should **not** be performed, due to a lack of clinical experience and a risk of attaining toxic blood levels of ROPIVACAINE FRESENIUS.

It is essential that aspiration for blood, or cerebrospinal fluid (where applicable), be done prior to injecting any local anaesthetic, both the original dose and all subsequent doses, to avoid intravascular or subarachnoid injection. A negative aspiration does however not ensure against an intravascular or subarachnoid injection.

ROPIVACAINE FRESENIUS should be used with caution in patients receiving local anaesthetics and substances structurally related to amide-type local anaesthetics, since the toxic effects of these medicines are additive (see section 4.5).

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 may lead to high plasma concentrations.

ROPIVACAINE FRESENIUS 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.

When neuraxial anaesthesia (epidural/spinal anaesthesia) is employed, patients who are anti-coagulated or are scheduled to be anti-coagulated with low molecular weight heparins or heparinoids are at risk of developing an epidural or spinal haematoma which may result in long-term or permanent paralysis.

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

The safety and efficacy of ROPIVACAINE FRESENIUS depends on proper dosage, correct technique and adequate precautions. Consult standard textbooks regarding specific techniques and precautions for various regional anaesthetic procedures.

Use the lowest dosage that results in effective anaesthesia (see section 4.2).

Use ROPIVACAINE FRESENIUS with caution in patients with known sensitivity for medicines. A possible cross-hypersensitivity with other amide-type local anaesthetics should also be considered (see section 4.3).

Careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness should be accomplished after each ROPIVACAINE FRESENIUS 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.

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

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

Patients treated with antidysrhythmic medicines class III (e.g. amiodarone) should be under close surveillance and electrocardiogram (ECG) monitoring should be considered, since cardiac effects may be additive (see section 4.5).

There have been reports of cardiac arrest during the use of ROPIVACAINE FRESENIUS for epidural anaesthesia or peripheral nerve blockade, especially after unintentional intravascular administration in elderly patients and in patients with concomitant heart disease. In some instances, resuscitation has been difficult. Should cardiac arrest occur, prolonged resuscitative efforts may be required to improve the possibility of a successful outcome.

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. The risk should also be considered in patients suffering from malnutrition or patients with hypovolaemia.
Patients with hypovolaemia due to any cause may develop sudden and severe hypotension during epidural anaesthesia, regardless of the local anaesthetic used (see section 4.5).

Epidural and intrathecal anaesthesia may lead to hypotension and bradycardia. Treat hypotension promptly with a sympathomimetic intravenously, repeat as necessary and supplement with an adequate vascular filling if necessary.

Avoid prolonged administration of ROPIVACAINE FRESENIUS in patients concomitantly treated with strong CYP1A2 inhibitors, such as fluvoxamine and enoxacin (see section 4.5).

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

Chondrolysis
There have been reports of chondrolysis in patients receiving postoperative intra-articular continuous infusion of local anaesthetics, including ROPIVACAINE FRESENIUS. Most 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 FRESENIUS should be avoided, as the efficacy and safety has not been established.

Paediatric population
The safety and efficacy of ROPIVACAINE FRESENIUS 2 mg/ml for field block in children up to and including 12 years has not been established.
The safety and efficacy of ROPIVACAINE FRESENIUS 7,5 mg/ml and 10 mg/ml in children up to and including 12 years has not been established.
The safety and efficacy of ropivacaine 2 mg/ml for peripheral nerve blocks in infants below 1 year has not been established.

Porphyria
ROPIVACAINE FRESENIUS is possibly porphyrinogenic and should only be prescribed to patients with acute porphyria when no safer alternative is available. Appropriate precautions should be taken for all porphyric patients.

Excipients with recognised action/effect
ROPIVACAINE FRESENIUS contains sodium chloride. This should be considered in patients on a controlled sodium diet:

ROPIVACAINE 2 mg/ml INJECTION FRESENIUS solution for injection contains 3,4 mg sodium per ml, equivalent to 0,17 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

ROPIVACAINE 2 mg/ml INFUSION FRESENIUS solution for infusion contains 3,4 mg sodium per ml, equivalent to 0,17 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
ROPIVACAINE 5 mg/ml INJECTION FRESENIUS solution for injection contains 3,17 mg of sodium per ml, equivalent to 0,15 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

ROPIVACAINE 7,5 mg/ml INJECTION FRESENIUS solution for injection contains 2,99 mg sodium per ml, equivalent to 0,15 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

ROPIVACAINE 10 mg/ml INJECTION FRESENIUS solution for injection contains 2,8 mg sodium per ml, equivalent to 0,14 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interactions with other medicines and other forms of interaction

Local anaesthetics and antidysrhythmic medicines
ROPIVACAINE FRESENIUS should be used with caution in patients receiving other local anaesthetics or medicines structurally related to amide-type local anaesthetics, e.g., certain antiarrhythmics, such as lidocaine (lignocaine) and mexiletine, since the systemic toxic effects are additive.

Simultaneous use of ROPIVACAINE FRESENIUS with general anaesthetics or opioids may potentiate each other's adverse effects. Specific interaction studies with ropivacaine and antiarrhythmic medicines class III (e.g. amiodarone) have not been performed, but caution is advised (see section 4.4).

CYP1A2 inhibitors

Cytochrome P450 (CYP) 1A2 is involved in the formation of 3-hydroxy ropivacaine, the major metabolite. *In vivo* the plasma clearance of ropivacaine is reduced during co-administration of fluvoxamine, a selective and potent CYP1A2 inhibitor. Thus, strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin, given concomitantly during prolonged administration of ROPIVACAINE FRESENIUS, may interact with ROPIVACAINE FRESENIUS. Prolonged administration of ropivacaine should be avoided in patients concomitantly treated with strong CYP1A2 inhibitors (see section 4.4).

CYP3A4 inhibitors

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

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

4.6 Fertility, pregnancy and lactation

The safe use of ROPIVACAINE FRESENIUS during lactation and pregnancy, other than by those in labour, has not been established. The use of ROPIVACAINE FRESENIUS is therefore not recommended.

Pregnancy

Foetal bradycardia frequently follows paracervical block with some amide-type local anaesthetics such as ROPIVACAINE FRESENIUS and may be associated with foetal acidosis (see section 4.3). Added risk appears to be present in prematurity, toxaemia of pregnancy and foetal distress.

Lactation

No data are available on the excretion of ropivacaine into human breast milk.

4.7 Driving and the use of machinery

Besides the direct anaesthetic effect, ROPIVACAINE FRESENIUS may influence mental function and co-ordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

General

The effects of systemic overdose and unintentional intravascular injections can be serious (see section 4.9).

In children the most frequently reported adverse events (> 1 %) are vomiting, nausea and pruritus. ROPIVACAINE FRESENIUS may cause acute toxic effects after high doses or if very rapidly rising blood levels occur due to accidental intravascular injection or overdose. Convulsions has been reported after an unintended intravascular injection at an attempted brachial plexus block with 200 mg.

Side effects reported after use of ropivacaine (as in ROPIVACAINE FRESENIUS) include physiological effects of the nerve block itself, e.g. hypotension, bradycardia and urinary retention after epidural and intrathecal block, and events caused directly by needle puncture (e.g. spinal haematoma, postdural puncture headache), or indirectly by introduction of micro-organisms (e.g. meningitis and epidural abscess).

The number of patients that can be expected to experience side effects varies with the route of administration. Systemic adverse reactions usually occur due to inadvertent intravascular injection, excessive dose or rapid absorption.

Tabulated list of adverse reactions

System organ class	**Frequency**	**Side effect**
Immune system disorders	*Less frequent*	Allergic reactions (anaphylactic reactions, angioedema and urticaria)
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, dysarthria, muscular twitching, tremor)*, hypoaesthesia
	Frequency unknown	Dyskinesia
Cardiac disorders	*Frequent*	Bradycardia, tachycardia
	Less frequent	Cardiac arrest, cardiac dysrhythmias
Vascular disorders	*Frequent*	Hypotension (less frequent in children), hypertension
	Less frequent	Syncope
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Dyspnoea
Gastrointestinal disorders	*Frequent*	Nausea, vomiting (more frequent in children)
Musculoskeletal and connective tissue disorders	*Frequent*	Back pain
Renal and urinary disorders	*Frequent*	Urinary retention
General disorders and administrative site conditions	*Frequent*	Temperature elevation, rigour, chills
	Less frequent	Hypothermia

* These symptoms usually occur because of inadvertent intravascular injection, overdose or rapid absorption.

Class-related side effects:

This section includes complications related to the anaesthetic technique regardless of the local anaesthetic used.

Neurological complications

Neuropathy and spinal cord dysfunction (e.g. anterior spinal artery syndrome, arachnoiditis, cauda equina damage), have been associated with epidural anaesthesia.

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 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 medicine, both quantitatively and qualitatively.

Central nervous system toxicity

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

Recovery follows the redistribution of the local anaesthetic medicine from the CNS and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the medicine have been injected.

Cardiovascular system toxicity

Cardiovascular toxicity indicates a more severe situation. Hypotension, bradycardia, dysrhythmia and even cardiac arrest may occur because of high systemic concentrations of local anaesthetics. The intravenous infusion of ropivacaine (as in ROPIVACAINE FRESENIUS) results in signs of depression of conductivity and contractility.

Cardiovascular toxic effects are generally preceded by signs of toxicity in the CNS unless the patient is receiving a general anaesthetic or is heavily sedated with medicines 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 section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care 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://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

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

Acute systemic toxicity:

Systemic toxic reactions primarily involve the CNS and the 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.

Central nervous system toxicity:

CNS toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are usually light-headedness, circumoral paraesthesia, numbness of the tongue, hyperacusis, tinnitus and visual disturbances. Dysarthria, muscular twitching or tremors are more serious and precede the onset of generalised convulsions. These signs should not be mistaken for neurotic behaviour. Unconsciousness and grand mal convulsions may follow which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with respiration and possible loss of functional airways. In severe cases apnoea may occur. Acidosis hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

Recovery is due to redistribution of ROPIVACAINE FRESENIUS from the CNS and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the medicine have been injected.

Cardiovascular system toxicity:

CVS toxicity may be seen in severe cases and is generally preceded by signs of toxicity in the CNS. In patients under heavy sedation or receiving a general anaesthetic, prodromal CNS symptoms may be absent. Hypotension, bradycardia, dysrhythmia and even cardiac arrest may occur because of high systemic concentrations of local anaesthetics, but 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 they may be under general anaesthesia.

Treatment:

If signs of acute systemic toxicity appear, injection or infusion of ROPIVACAINE FRESENIUS should be stopped immediately and central nervous symptoms (such as convulsions and CNS depression) should be promptly treated with the appropriate~~d~~ airway/respiratory support and the administration of anticonvulsant medicines.

Should circulatory arrest 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 is evident (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, and/or inotropic medicines should be considered. Children should be given doses corresponding to their 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: N01B B09

Category and class: A 4 Local anaesthetics

Ropivacaine is a long-acting, amide-type local anaesthetic, developed as an S-enantiomer.

At high doses ropivacaine produces surgical anaesthesia, while at lower doses it produces sensory block (analgesia), with limited and non-progressive motor block.

The onset and duration of the local anaesthetic effect of ropivacaine depend on the dose and site of administration. The presence of a vasoconstrictor (e.g. epinephrine (adrenaline)) has little, if any influence.

Ropivacaine causes reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions though the cell membrane of the nerve fibres.

Local anaesthetics, including ropivacaine, may have similar effects on other excitable membranes e.g. in the brain and myocardium. If excessive amounts of the ropivacaine reach the systemic circulation rapidly, symptoms and signs of toxicity may appear, emanating from the central nervous and cardiovascular systems.

Indirect cardiovascular effects (hypotension, bradycardia) may occur after epidural administration, depending on the extent of the concomitant sympathetic block.

5.2 Pharmacokinetic properties

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

Ropivacaine shows complete and biphasic absorption from the epidural space with half-lives of the 2 phases of the order of 14 minutes and 4 hours. The slow absorption is the rate-limiting factor in the elimination of ropivacaine.

After IV administration, ropivacaine has a mean total plasma clearance in the order of 440 ml/minute, an unbound plasma clearance of 8 litres/minute, a renal clearance of 1 ml/minute, a volume of distribution at steady state of 47 litres and a terminal half-life of 1,8 hours.

Ropivacaine has an intermediate hepatic extraction ratio of about 0,4. It is mainly bound to alpha-1-acid glycoprotein in plasma with an unbound fraction of about 6 %.

An increase in total plasma concentrations during continuous epidural and interscalene infusion has been observed, related to a postoperative increase of alpha-1-acid

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

Ropivacaine readily crosses the placenta and equilibrium regarding 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.

Ropivacaine is extensively metabolised in the liver, predominantly by aromatic hydroxylation to 3-hydroxy-ropivacaine, mediated by cytochrome P4501A2 and N-dealkylation to PPX mediated by CYP3A4. After single IV administration approximately 37 % of the total dose is excreted in the urine, as both free and conjugated 3-hydroxy-ropivacaine, the major metabolite. Low concentrations of 3-hydroxy-ropivacaine have been found In the plasma. Urinary excretion of the PPX and other metabolites account for less than 3 % of the dose. The metabolites have less activity than ropivacaine.

During epidural infusion, both PPX and 3-hydroxy-ropivacaine are the major metabolites excreted in the urine. A similar pattern of metabolites has been found in children above 1 year of age.

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

Special populations

Impaired renal function

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 when 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.

Elderly patients

No information available.

Paediatric patients

In children aged between 1 and 12 years ropivacaine pharmacokinetics after regional anaesthesia have been shown to be unrelated to age. In this group ropivacaine has a total plasma clearance in the order of 7,5 ml/min/kg, an unbound plasma clearance of 0,15 litre/min/kg, a volume of distribution at steady state of 2,4 L/kg, an unbound fraction of 5 % and a terminal half-life of 3 hours. Ropivacaine shows a biphasic absorption from the caudal space. The clearance related to body weight in this age group is similar to that in adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injection

6.2 Incompatibilities

In alkaline solutions precipitation may occur as ropivacaine is poorly soluble above pH 6,0.

Solution for injection:

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

Solution for infusion:

Compatibilities with solutions other than those mentioned in section 6.6 have not been investigated.

6.3 Shelf-life

Shelf-life before opening

3 years (solution for injection) - polypropylene ampoule

2 years (solution for infusion) - ***Free****flex*® bags

Shelf-life after first 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.

For shelf-life of mixtures see section 6.6.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Do not refrigerate or freeze

For single use only. Discard any unused portion.

For storage conditions after first opening, see section 6.3.

6.5 Nature and contents of container

ROPIVACAINE 2 mg/ml INJECTION FRESENIUS is available in a 10 ml and 20 ml transparent blow moulded polypropylene ampoule (*Ovalia)* with an integrated Luer-lock fitting.

ROPIVACAINE 5 mg/ml INJECTION FRESENIUS is available in a 10 ml transparent blow moulded polypropylene ampoule (*Ovalia*), with an integrated Luer-lock fitting.

ROPIVACAINE 7,5 mg/ml INJECTION FRESENIUS is available in a 10 ml and 20 ml transparent blow moulded polypropylene ampoule (*Ovalia*), with an integrated Luer-lock fitting.

ROPIVACAINE 10 mg/ml INJECTION FRESENIUS is available in a 10 ml and 20 ml transparent blow moulded polypropylene ampoule (*Ovalia*), with an integrated Luer-lock fitting.

ROPIVACAINE 2 mg/mL INFUSION FRESENIUS is available in a 100 ml or 200 ml transparent, polyolefin bag (***Free****flex*®), with an infusion port and injection port consisting of a polypropylene housing and an overpouch based on polyolefins.

1, 5, 10 ampoule(s) are packed in a blister pack. All the ampoules are packed in an outer carton.

The ***Free****flex*® bags are packed in an overwrap pouch in a pack of 5's.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

ROPIVACAINE FRESENIUS products are preservative free and are intended for single use only. Discard any unused solution.
The product should be visually inspected prior to use. The solution should only be used if it is clear, practically free from particles and if the container is undamaged.
The intact container must not be re-autoclaved.

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

7. REGISTRATION HOLDER

Fresenius Kabi South Africa (Pty) Ltd
Stand 7, Growthpoint Business Park
162 Tonetti Street
Halfway House
Midrand
1685

8. REGISTRATION NUMBERS

ROPIVACAINE 2 mg/ml INFUSION FRESENIUS: 46/4/0899
ROPIVACAINE 2 mg/ml INJECTION FRESENIUS: 46/4/0900
ROPIVACAINE 5 mg/ml INJECTION FRESENIUS: 46/4/0901
ROPIVACAINE 7,5 mg/ml INJECTION FRESENIUS: 46/4/0902
ROPIVACAINE 10 mg/ml INJECTION FRESENIUS: 46/4/0903

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

26 October 2021

10. DATE OF REVISION OF THE TEXT