Central Administration for Pharmaceutical care Approval Date: 20/ 11/2024 Revisor: Dr.yasmin
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to:Mhra

Ropivacaine SLS Solution for infusion
Ropivacaine hydrochloride 2mg/ml
Solution for infusion

1 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ropivacaine 2 mg/ml.

Each ml solution for infusion contains 2 mg ropivacaine hydrochloride. Each 100 ml bag contains Ropivacaine HCl monohydrate 211.4 mg (Eq. to Ropivacaine HCl 1 mg) = 200 mg
Excipients with known effect:
Each 100 ml bag contains 337.98 mg of-sodium For the full list of excipients, see section 6.1.

2 PHARMACEUTICAL FORM

Solution for infusion.

The medicinal product is a clear, Colorless solution.

3 CLINICAL PARTICULARS

3.1 Therapeutic indications

Ropivacaine SLS 2 mg/ml is indicated for acute pain management

In adults and adolescents over 12 years of age for:
- Continuous epidural infusion during postoperative pain or labour pain;
- Field blocks;
- Continuous peripheral nerve block via a continuous infusion , e.g. postoperative pain management.

In infants from 1 year and children aged 12 years or less (per- and postoperative):
- Single and continuous peripheral nerve block.

In neonates, infants and children aged 12 years or less for (per- and postoperative):
- Caudal epidural block.
- Continuous epidural infusion

Dr/yasmin

3.2 *Posology and method of administration*

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

Posology

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

Table 1: Adults and adolescents over 12 years of age:

	Conc. mg/ml	Volume ml	Dose mg	Onset minutes	Duration hours
ACUTE PAIN MANAGEMENT					
Lumbar Epidural Administration					
Bolus	2.0	10-20	20-40	10-15	0.5-1.5
Intermittent injections (top-up) (e.g. labour pain management)	2.0	10-15 (minimum interval 30 minutes)	20-30		
Continuous infusion, e.g. labour pain	2.0	6-10 mL/h	12-20 mg/h	n/a	n/a
Postoperative pain management	2.0	6-14 ml/h	12-28 mg/h	n/a	n/a
Thoracic Epidural Administration					
Continuous infusion (postoperative pain management)	2.0	6-14 mL/h	12-28 mg/h	n/a	n/a
Field Block					

(e.g. minor nerve block and infiltration)	2.0	1-100	2-200	1-5	2-6
Peripheral Nerve Block					
(Femoral or interscalene block) Continuous infusion or intermittent injections (e.g. postoperative pain management)	2.0	5-10 ml/h	10-20 mg/h	n/a	n/a
The doses in the table are those considered to be necessary to produce a successful block and should be regarded as guidelines for use in adults. Individual variations in onset and duration occur. The figures in the column 'Dose' reflect the expected average dose range needed. Standard textbooks should be consulted for both factors affecting specific block techniques and individual patient requirements. n/a = not applicable					

Method of administration

Perineural and epidural administration by infusion.

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

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

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

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with only mild and non- progressive motor block in most cases of moderate to severe postoperative pain. The maximum duration of the epidural block is 3 days. However, close monitoring of analgesic effect should be performed in order to remove the catheter as soon as the pain condition allows it. With this technique a significant reduction in the need for opioids has been observed.

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

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

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

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

6 to 12 months			
Bolus dose[a]	2.0	0.5 – 1	1 -2
Infusion up to 72 hours	2.0	0.2 ml/kg/h	0.4 mg/kg/h
1 to 12 years			
Bolus dose[b]	2.0	1	2
Infusion up to 72 hours	2.0	0.2 ml/kg/h	0.4 mg/kg/h

The dose in the table should be regarded as guidelines for use in paediatrics. Individual variations occur. In children with a high body weight a gradual reduction of the dosage is often necessary and should be based on the ideal body weight. The volume for single caudal epidural block and the volume for epidural bolus doses should not exceed 25 mL in any patient. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

a Doses in the low end of the dose interval are recommended for thoracic epidural blocks while doses in the high end are recommended for lumbar or caudal epidural blocks.
b Recommended for lumbar epidural blocks. It is good practice to reduce bolus doses for thoracic epidural analgesia.

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

Table 3: Peripheral nerve blocks. Infants and children aged 1-12 years

	Conc.	Volume	Dose
	mg/ml	ml/kg	mg/kg
ACUTE PAIN MANAGEMENT (per- and postoperative)			
Single injections for peripheral nerve block	2.0	0.5 – 0.75	1.0 – 1.5
e.g.iliolingual nerve block, brachial plexus block, fascia iliaca compartment block	2.0	0.5 – 1.5	1.0 – 3.0
Multiple blocks	2.0	0.1 – 0.3 ml/kg/h	0.2 – 0.6 mg/kg/h
Continuous infusion for peripheral nerve block in children 1 to 12 years. Infusion up to 72 hours			

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

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

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

Method of administration

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

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

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

Ropivacaine SLS Solution for infusion is only administered by infusion route , so for doses cannot be achieved by its adminsteration route , use other suitable pharmaceutical dosage form for Ropivacaine hydrochloride 2mg/ml

3.3 Contraindications

Hypersensitivity to active substance or to any of the excipients listed in section 6.1 or to other local anaesthetics of the amide type.
General contraindications related to epidural anaesthesia, regardless of the local anaesthetic used, should be taken into account.

Intravenous regional anaesthesia.
Obstetric paracervical anaesthesia.
Hypovolaemia.

3.4 Special warnings and precautions for use

Regional anaesthetic procedures should always be performed in a properly equipped and staffed area. Equipment and drugs necessary for monitoring and emergency resuscitation should be immediately available. The clinician responsible should take the necessary precautions to avoid intravascular injection (see section 4.2) and be appropriately trained and familiar with diagnosis and treatment of 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. 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
Epidural and intrathecal anaesthesia may lead to hypotension and bradycardia. Hypotension should be treated promptly with a vasopressor intravenously, and with an adequate vascular filling.

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

There have been rare reports of cardiac arrest during the use of ropivacaine for epidural anaesthesia or peripheral nerve blockade, especially after unintentional 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 block
Major peripheral nerve blocks may imply the administration of a large volume of local anaesthetic in highly vascularized areas, often close to large vessels where there is an increased risk of intravascular injection and/or rapid systemic absorption, which can lead to high plasma concentrations.

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

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

Patients in poor general health

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

Patients with hepatic and renal impairment
Ropivacaine is metabolised in the liver and should therefore be used with caution in patients with severe liver disease; repeated doses may need to be reduced due to delayed elimination.

Normally there is no need to modify the dose in patients with impaired renal function when used for single dose or short-term treatment. Acidosis and reduced plasma protein concentration, frequently seen in patients with chronic renal failure, may increase the risk of systemic toxicity.

Acute porphyria
Ropivacaine solution for infusion 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, including ropivacaine. The majority of reported cases of chondrolysis have involved the shoulder joint. Intra-articular continuous infusion is not an approved indication for ropivacaine. Intra-articular continuous infusion with ropivacaine should be avoided, as the efficacy and safety has not been established.

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

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, SpO_2) and local neurotoxicity (e.g. prolonged recovery) is required, which should be continued after ending infusion, due to a slow elimination in neonates.

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

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

Excipients with known effect
This medicinal product contains 337.98 mg sodium per ml
Ropivacaine 2 mg/ml is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

3.5 Interaction with other medicinal products and other forms of interaction

Ropivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, e.g. certain antiarrhythmics, such as lidocaine and mexiletine, since the systemic toxic effects are additive. Simultaneous use of ropivacaine with general anaesthetics or opioids may potentiate each others' (adverse) effects. Specific interaction studies with ropivacaine and anti-arrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution is advised (see also section 4.4). Cytochrome P450 (CYP) 1A2 is involved in the formation of 3-hydroxy- ropivacaine, the major metabolite. *In vivo,* the plasma clearance of ropivacaine was reduced by up to 77% during co-administration of fluvoxamine, a selective and potent CYP1A2 inhibitor. Thus strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin, given concomitantly during prolonged administration of ropivacaine, can interact with ropivacaine.
Prolonged administration of ropivacaine should be avoided in patients concomitantly treated with strong CYP1A2 inhibitors, see also section 4.4.

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

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

3.6 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.

Breast-feeding
There are no data available concerning the excretion of ropivacaine into human milk.

Fertility
There are no data available concerning the fertility.

3.7 Effects on ability to drive and use machines

No data are available. 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 alertness.

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3.8 Undesirable effects
General
The adverse reaction profile for ropivacaine is similar to those for other long acting local anaesthetics of the amide type. Adverse drug reactions should be distinguished from the physiological effects of the nerve block itself e.g. a decrease in blood pressure and bradycardia during spinal/epidural block.

Table 4: Table of adverse drug reactions
The frequencies used in the table in Section 4.8 are: very common (≥1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Undesirable Effect
Immune system disorders	Rare	Allergic reactions (anaphylactic reactions, angioneurotic oedema and urticaria)
Psychiatric disorders	Uncommon	Anxiety
Nervous System disorders	Common	Paraesthesia, Dizziness, Headache
	Uncommon	Symptoms of CNS toxicity (Convulsions, Grand mal convulsions, Seizures, Light headedness, Circumoral paraesthesia, Numbness of the tongue, Hyperacusis, Tinnitus, Visual disturbances, Dysarthria, Muscular twitching, Tremor)*, Hypoaesthesia
	Not known	Dyskinesia
Cardiac disorders	Common	Bradycardia, Tachycardia
	Rare	Cardiac arrest, Cardiac arrhythmias
Vascular disorders	Very common	Hypotension[a]
	Common	Hypertension
	Uncommon	Syncope
Respiratory, Thoracic and Mediastinal disorders	Uncommon	Dyspnoea
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting[b]
Musculoskeletal and connective tissue disorders	Common	Back pain
Renal and Urinary disorders	Common	Urinary retention
General disorders and Administrative site conditions	Common	Temperature elevation, Chills
	Uncommon	Hypothermia

[a] Hypotension is less frequent in children (>1/100).

[b] Vomiting is more frequent in children (>1/10).

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

Class-related adverse drug reactions

Neurological complications

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

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

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

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

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

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

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as benzodiazepines or barbiturates. 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.

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

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

Treatment of acute systemic toxicity
See section 4.9.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via The Egyptian Pharmaceutical Vigilance Center directly on hotline 15301 or by sending an e-mail to: pv.followup@edaegypt.gov.eg

3.9 Overdose

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

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

If circulatory arrest should occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

If cardiovascular depression occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, and or inotropic agents should be considered. Children should be given doses commensurate with age and weight.

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

4 PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, local, Amides
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 Table 1 under posology and method of administration.

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.

4.2 Pharmacokinetic properties

Absorption
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 that of ropivacaine.

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

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

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

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

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

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

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

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

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

Paediatrics
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 Table 5 are those not affected by the postoperative increase in AAG.

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

Age Group	BW[a]	Clu[b]	Vu[c]	CL[d]	t1/2[e]	t1/2ppx[f]
	kg	(L/h/kg)	(L/kg)	(L/h/kg)	(h)	(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 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.

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

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

Age group	Dose	Cumax[a]	tmax[b]	Cumax[c]
	(mg/kg)	(mg/L)	(h)	(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 to 6 months compared to older children, which is related to the immaturity of their liver function. However, this is partly compensated for by the recommended 50% lower dose rate for continuous infusion in infants below 6 months.

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

Simulations on the sum of unbound plasma concentrations of ropivacaine and PPX, based on the PK parameters and their variance in the population analysis, indicate that for 1- to 12- year-old infants and children receiving 3

mg/kg single peripheral (ilioinguinal) nerve block the median unbound peak concentration reached after 0.8 h is 0.0347 mg/L, one-tenth of the toxicity threshold (0.34 mg/L). The upper 90% confidence interval for the maximum unbound plasma concentration is 0.074 mg/L, one-fifth of the toxicity threshold. Similarly, for

continuous peripheral block (0.6 mg ropivacaine/kg for 72 h) preceded by a 3mg/kg single peripheral nerve block, the median unbound peak concentration is 0.053 mg/L. The upper 90% confidence interval for the maximum unbound plasma concentration is 0.088 mg/L, one- quarter of the toxicity threshold.

5 PHARMACEUTICAL PARTICULARS

5.1 List of excipients

Sodium chloride
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

5.2 Incompatibilities

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

In alkaline solutions precipitation may occur as ropivacaine shows poor solubility at pH >6.

5.3 Shelf life

See outer pack

Shelf life after first opening: used immediately after opening.

5.4 Special precautions for storage

Un opened :Do not store above 30 ° C. Do not freeze.

After opening :used immediately after opening.

5.5 Nature and contents of container

Carton box contains single use Transparent Plastic Polypropylene bag with 2 SFC system (2 SFC port and 2 SFC cap which made of Polypropylene (PP) assembled with rubber disc type I Which made of Polyisoprene Type I free of natural rubber and free of 2 MBT and Nitrosamines) of 100 ml solution containing Ropivacaine hydrochloride 2 mg / ml with outer label.

1.1 Special precautions for disposal

Ropivacaine products are preservative-free and are intended for single use only. Discard any

unused solution.

Ropivacaine solution for infusion in polyolefin infusion bags is chemically and physically compatible with the following drugs:

Concentration of Ropivacaine: 1-2 mg/ml	
Additive	**Concentration***
Fentanyl citrate	1.0 - 10.0 microgram/ml
Sufentanil citrate	0.4 - 4.0 microgram/ml
Morphine sulfate	20.0 - 100 microgram/ml
Clonidine hydrochloride	5.0 - 50 microgram/ml

* The concentration ranges stated in the table are wider than those used in clinical practice. Epidural infusions of ropivacaine/sufentanil citrate, ropivacaine/morphine sulphate and ropivacaine/clonidine hydrochloride have not been evaluated in clinical studies.

The medicinal product should be visually inspected prior to use. The solution should only be used if it is clear, practically free from particles and if the container is undamaged.

From a microbiological point of view, the mixtures should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user, unless dilution has taken place in controlled and validated aseptic conditions.

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

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Manufacturer : El-Nasr for Pharmaceutical Chemicals for Human, veterinary and medical device