ROPIVAPLIN

Ropivacaine Hydrochloride Solution for Injection or infusion USP, 2 mg/mL

1. NAME OF THE MEDICINAL PRODUCT

ROPIVAPLIN - Ropivacaine Hydrochloride Solution for Injection or Infusion USP, 2 mg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains Ropivacaine hydrochloride USP 2 mg,

For a full list of excipients, see 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Solution for Injection or Infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ropivacaine Hydrochloride Injection 7.5mg/mL

Surgical anaesthesia:

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

Acute pain management:

- Continuous epidural infusion or intermittent bolus administration e.g. postoperative or labour pain.
- Field block

Ropivacaine Hydrochloride Solution for Injection or infusion USP, 2 mg/mL:

Acute pain relief (peri- and postoperative) in children:

- Caudal epidural block in infants (>30 days old) and children up to and including 12 years.
- Continuous epidural infusion in infants (>30 days old) and children up to and including 12 years.

4.2 Posology and method of administration

Ropivacaine Hydrochloride Solution for Injection or Infusion USP, should only be used by, or under the supervision of, clinicians experienced in regional anaesthesia.

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 of Ropivacaine Hydrochloride Solution for Injection or Infusion USP, is generally recommended.

Dosage and recommendations for Ropivacaine Hydrochloride Solution for Injection or Infusion USP, in adults and children above 12 years of age.

	Conc	Volume	Dose	Onset	Duration
	mg/mL	mL	mg	min-	hours
SURGICAL ANAESTHESIA					
Lumbar epidural Administration					
Surgery	7.5	15-25	113-188	10-20	3-5
Caesarean Section	7.5	15-20	113-150	10-20	3-5
Thoracic Epidural Administration					
To establish block for postoperative pain relief	7.5	5-15 (depending on the level of injection)	38-113	10-20	n/a(2)
Major Nerve Block (e.g. brachial plexus)	7.5	30-40	225-300	10-25	6-10
Field Block (e.g. Minor nerve blocks and infiltration)	7.5	1-30	7.5-225	1-15	2-6
ACUTE PAIN MANAGEMENT					
Lumbar Epidural Administration					
Bolus	2	10-20	20-40	10-15	0.5-1.5
Intermittent injections (top-up) (e.g. labour pain management)	2	10-15 (minimum intervals 30 mins)	20-30	--	--
Continuous infusion e.g. Labour pain	2	6-10 mL/h	12-20 mg/h	n/a (2)	n/a (2)
Postoperative pain management	2	6-14 mL/h	12-28 mg/h	n/a (2)	n/a (2)
Thoracic Epidural Administration Continuous infusion (postoperative pain management)	2	6-14 mL/h	12-28 mg/h	n/a (2)	n/a (2)
Field Block					
e.g. minor nerve blocks and infiltration	2	1-100	2-200	1-5	2-6

The doses in the table are those considered to be necessary to produce a successful block and should be regarded as guidelines for use in adults. Individual variations in onset and duration occur. The figures in the column 'Dose' reflect the expected average dose range needed. Standard textbooks should be consulted for both factors affecting specific block techniques and individual patient requirements.
(1) Incremental dosing should be applied, the starting dose of about 100 mg (97.5 mg = 13 mL; 105 mg = 14 mL) to be given over 3-5 minutes. Two additional doses, each of 25 mg, may be administered as needed. The total administered dose should not exceed 150 mg.
(2) n/a = not applicable
(3) The dose for a major nerve block must be adjusted according to site of administration and patient status. Supraclavicular brachial plexus blocks may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used.

Method of administration

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 25-30 mg/min, while closely observing the patient's vital functions and maintaining verbal contact. When an epidural dose is to be injected, a preceding test dose of 3-5 mL lidocaine (lignocaine) with adrenaline (Xylocaine 1-2% with Adrenaline 1:200,000) is recommended. An inadvertent intravascular injection may be recognised by a temporary increase in heart rate and an accidental intrathecal injection by signs of a spinal block.

If toxic symptoms occur, the injection should be stopped immediately.

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

When prolonged blocks are used, either through continuous infusion or through repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. Cumulative doses up to 675 mg Ropivacaine 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 Hydrochloride Injection 7.5 mg/ml is induced via an epidural catheter. Analgesia is maintained with Ropivacaine Hydrochloride Solution for Infusion, USP 2 mg/mL. Infusion rates of 6-14 mL (12- 28 mg) per hour provide adequate analgesia with only slight and non-progressive motor block in most cases of moderate to severe postoperative pain. The maximum duration of epidural block is 3 days. However, close monitoring of analgesic effect should be performed in order to remove the catheter as soon as the pain condition allows it. With this technique, a significant reduction in the need for opioids has been observed.

In clinical studies an epidural infusion of Ropivacaine Hydrochloride Solution for Injection or infusion, USP 2 mg/mL alone or mixed with fentanyl 1-4 microgram/mL has been given for postoperative pain management for up to 72 hours. Ropivacaine Hydrochloride Solution for Injection or infusion, USP 2 mg/mL (6-14 mL/hour) provided adequate pain relief for the majority of patients. The combination of Ropivacaine Hydrochloride Solution for Injection or Infusion USP, and fentanyl provided improved pain relief but caused opioid side effects. The combination of Ropivacaine Hydrochloride Solution for Injection or Infusion USP, and fentanyl has been investigated only for Ropivacaine Hydrochloride Solution for Injection or infusion, USP 2 mg/mL.

For Caesarean section, neither intrathecal administration nor the use of the ropivacaine concentration 10 mg/mL for epidural administration, have been documented.

Ropivacaine Hydrochloride Injection or infusion USP, 2 mg/mL:

Children (>30 days old and up to and including 12 years)

	Strength mg/mL	Volume mL/kg	Dose mg/kg
ACUTE PAIN MANAGEMENT (Peri and Postoperative)			
Single Caudal Epidural Block in Children >30 days old and up to and including 12 years			
Blocks below T12, in children with a body weight up to 25 kg	2 mg/mL	1 mL/kg	2 mg/kg
Continuous Epidural Infusion In children with a body weight up to 25 kg			
>30 days old and up to 6 months			
Bolus dose[a]	2 mg/mL	0.5-1 mL/kg	1-2 mg/kg
Infusion up to 72 hours	2 mg/mL	0.1 mL/kg/h	0.2 mg/kg/h
6 up to 12 months			
Bolus dose[a]	2 mg/mL	0.5-1 mL/kg	1-2 mg/kg
Infusion up to 72 hours	2 mg/mL	0.2 mL/kg/h	0.4 mg/kg/h
1 to 12 years			
Bolus dose[b]	2 mg/mL	1 mL/kg	2 mg/kg
Infusion up to 72 hours	2 mg/mL	0.2 mL/kg/h	0.4 mg/kg/h

[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.

The recommended strength of Ropivacaine Hydrochloride solution for injection /infusion for Single Caudal Epidural Block in children >30 days old and up to 12 years and for Continuous Epidural Infusion in children with a body weight up to 25 kg is 2 mg/mL.

The doses in the table should be regarded as recommendations when used in children. Individual variations occur. For overweight children a gradual reduction of the dosage, based on the ideal body weight, is often necessary. The volume for single caudal epidural block and the volume for epidural bolus doses should not exceed 25 mL in any patient.

Method of administration

To prevent inadvertent intravascular injections, great caution should be observed. Careful aspiration is recommended before and during injection of the total dose. The patient´s vital functions should be carefully monitored during the injection. Should toxic signs appear, the injection should be immediately stopped.

When administering the calculated dose, fractionation of the total dose is always recommended.

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. The volume of the caudal epidural injection may be adjusted to control the spread of the sensory block. Doses up to 3 mg/kg of a concentration of Ropivacaine 3 mg/mL have been used safely in children older than 4 years.

For children with a body weight over 25 kg there is limited experience of caudal blocks. The use of Ropivacaine in premature children has not been documented.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. Hypersensitivity to local anaesthetics of the amide type.

4.4 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.

Patients receiving major blocks should be in an optimal condition and have an i.v. line inserted before the blocking procedure. The clinician responsible should take the necessary precautions to avoid intravascular injection (see *Posology and method of administration*) and be appropriately trained and familiar with the diagnosis and treatment of side effects, systemic toxicity and other complications (see *Undesirable effects* and *Overdose*). One complication is 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.

Cardiovascular

Epidural and spinal anaesthesia may lead to hypotension and bradycardia. The risk of such effects can be reduced by injecting a vasopressor.

Hypotension should be treated promptly with a sympathomimetic intravenously, repeated as necessary.

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.

There have been rare reports of cardiac arrest during the use of Ropivacaine Hydrochloride Solution for Injection or Infusion USP, 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. Caution is required to prevent injections in inflamed areas.

Major peripheral nerve blocks

Major peripheral nerve blocks may imply the administration of a large volume of local anaesthetic in highly vascularised areas, often close to large vessels where there is an increased risk of intravascular injection and/or rapid systemic absorption, which can lead to high plasma concentrations.

Hypersensitivity

A possible cross – hypersensitivity with other amide – type local anaesthetics should be taken into account.

Hypovolaemia

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

Patients in poor general health

Patients in poor general condition due to ageing or other compromising factors such as partial or complete heart conduction block, advanced livery 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 Hydrochloride Solution for injection and infusion USP, 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.

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. Due to multiple contributing factors and inconsistency in the scientific literature regarding mechanism of action, causality has not been established. Intra-articular continuous infusion is not an approved indication for Ropivacaine Hydrochloride Solution for Injection or Infusion USP.

Excipients with recognised action / effect

This medicinal product contains maximum 3.7 mg sodium per mL. To be taken into consideration by patients on a controlled sodium diet.

Prolonged administration

Prolonged administration of Ropivacaine should be avoided in patients treated with strong inhibitors of CYP1A2, (such as fluvoxamine and enoxacin) (see *Interaction with other Medicinal Products and other forms of Interaction).*

Paediatric population

Neonates may need special attention due to immaturity of some organs and functions. This is especially important during continuous epidural infusion. Higher concentrations than 5 mg/mL have not been documented in children.

4.5 Interaction with other Medicinal Products and other forms of Interaction

Ropivacaine hydrochloride Solution for Injection or Infusion USP, 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.

Specific interactions studies with ropivacaine and anti-arrhythmics class III (e.g., amiodarone) have not been performed, but caution is advised (see *Special warnings and precautions for use).*

In healthy volunteers, ropivacaine clearance was reduced by up to 77% during co-administration of fluvoxamine, a potent competitive inhibitor of CYP1A2. CYP1A2 is involved in the formation of 3-hydroxy-ropivacaine, a major metabolite. Thus, strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin, given concomitantly with Ropivacaine Hydrochloride Solution for Injection or Infusion USP, can cause a metabolic interaction leading to an increased ropivacaine plasma concentration. Prolonged administration of ropivacaine should therefore be avoided in patients treated with strong inhibitors of CYP1A2, (see *Special warnings and precautions for use).*

4.6 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 pregnancy, embryonal/foetal development, parturition or postnatal development.

Spinal administration in caesarean section has not been documented

Lactation

It is not known whether ropivacaine passes into breast milk.

4.7 Effects on Ability to Drive and use Machines

Besides the direct anaesthetic effect, 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.

4.8 Undesirable Effects

The adverse reaction profile for Ropivacaine Hydrochloride Solution for Injection or Infusion USP, is similar to those for other amide local anaesthetics. Adverse reactions caused by the drug per se are difficult to distinguish from physiological effects of the nerve block (e.g. hypotension and bradycardia), and events caused directly (e.g. nerve trauma) or indirectly (e.g. epidural abscess) from needle puncture.

Undesirable effects (from all kinds of blockades):

The adverse reactions are displayed within each organ class with the following frequencies Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (<1/1,000).

Adults:

Organ System	Frequency	Adverse reaction
Psychiatric disorders	Uncommon	Anxiety
Cardiac disorders	Common	Bradycardia[a], Tachycardia, Hypertension
	Rare	Cardiac arrest, arrhythmias
Vascular disorders	Very common	Hypotension[c]
	Common	Hypertension
	Uncommon	Syncope
Nervous system disorders	Common	Paraesthesia, Dizziness, Headache[a]
	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)[b], Hypoaesthesia[a]
Respiratory, Thoracic and mediastinal disorders	Uncommon	Dyspnoea[a*]
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting[a,d]
Renal and urinary disorders	Common	Urinary retention[a]
General disorders and administration site conditions	Common	Temperature elevation, Rigor, Back pain
	Uncommon	Hypothermia[a*]
	Rare	Allergic reactions (Anaphylactic reactions, angioneurotic oedema and urticaria)

[a] These reactions are more frequent after spinal anaesthesia.

[b] These symptoms usually occur because of inadvertent intravascular injection, overdose or rapid absorption (see section Overdose).
[c] Hypotension is uncommon in children (>1/100).
[d] Vomiting is very common in children. (>1/10).

Class related adverse drug reactions

The adverse reactions below include complications related to the anaesthetic technique regardless of the local anaesthetic used.

Neurological complications

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

Total spinal block

Total spinal block may occur if an epidural dose is inadvertently administered intrathecally, or if a too large intrathecal dose is administered.

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 local anaesthetics, which may appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularised areas *(*see *Special warnings and precautions for use*). 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

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 and or tremors are more serious and precede the onset of generalized convulsions. These signs should not be mistaken for neurotic behaviour. Unconsciousness and grand mal convulsions may follow which may last for a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly following convulsions due to increased muscular, together with the interference with respiration and possible loss of functional airways. In severe cases even apnoea may occur. Acidosis, hyperkalemia, hypocalcemia and hypoxia increase and extend the toxic effects of local anaesthetics.

Recovery is due to 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 system toxicity may be seen in severe cases and is generally preceded by signs of toxicity in the central nervous system. In patients under heavy sedation or receiving a general anaesthetic, prodromal CNS symptoms may be absent. Hypotension, bradycardia, arrhythmia and also 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 (see *Special warnings and precautions for use*).

Treatment of acute systemic toxicity

See Overdose.

4.9 Overdose

Symptoms

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

Treatment

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

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

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

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

5. Pharmacological Properties

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: Local Anaesthetics

ATC code: N01B B09

Mechanism of Action

Ropivacaine is a long-acting, amide-type local anaesthetic with both anaesthetic and analgesic effects. At high doses it produces surgical anaesthesia, while at lower doses, it produces sensory block (analgesia) with limited and non-progressive motor block.

Onset and duration of the local anaesthetic effect of Ropivacaine Hydrochloride Solution for Injection or Infusion USP, depend on the dose and site of administration, while presence of a vasoconstrictor (e.g. adrenaline) has little, if any influence.

Ropivacaine, like other local anaesthetics, causes reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the cell membrane of the nerve fibres.

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

Cardiac effects measured in vivo in animal studies showed that ropivacaine has a lower cardiac toxicity than bupivacaine.

Pregnant ewes showed no greater sensitivity to systemic toxic effects of ropivacaine than non-pregnant ewes.

Healthy volunteers exposed to intravenous infusions of CNS toxic doses showed significantly less cardiac effects after ropivacaine than after bupivacaine.

Indirect cardiovascular effects (hypotension, bradycardia) may occur after epidural block, depending on the extent of concomitant sympathetic block, but is less pronounced in children.

5.2 Pharmacokinetic Properties

Ropivacaine has a chiral centre and is the pure S-(-)-enantiomer. Ropivacaine has a pKa of 8.1 and the distribution ratio of 141 (25°C n-octanol/phosphate-buffer with pH 7.4). The metabolites have a pharmacological activity that is less than that of ropivacaine.

Absorption

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

Distribution

Ropivacaine has a mean total plasma clearance of the order of 440 mL/min, an unbound plasma clearance of 8 L/min, a renal clearance of 1 mL/min a volume distribution at steady state of 47 L and a terminal half-life of 1.8h after iv administration. Ropivacaine has an intermediate hepatic extraction ratio of about 0.4. It is mainly bound to α_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 α_1-acid glycoprotein.

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

Ropivacaine readily crosses the placenta with equilibrium in regard to unbound concentration is 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.

Metabolism

Ropivacaine is extensively metabolised in the liver, predominantly by aromatic hydroxylation to 3-hydroxy-ropivacaine (mediated by CYP1A2) 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.

Elimination

During epidural infusion, both PPX and 3-hydroxy-ropivacaine are the major metabolites excreted in the urine. Total PPX concentration in the plasma was about half of that of total ropivacaine, however, mean unbound concentrations of PPX was about 7 to 9 times higher than that of unbound ropivacaine following continuous epidural infusion up to 72 hours. The threshold for CNS-toxic unbound plasma concentrations of PPX in rats is about twelve times higher than that of unbound ropivacaine.

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.

Paediatric Patients

The pharmacokinetics of ropivacaine was characterized in a pooled population PK analysis on data in 192 children between 0 and 12 years of age from six studies. 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.

Unbound ropivacaine clearance increases from 2.4 and 3.6 L/h/kg in the new born and the 1- month neonate to about 8-16 L/h/kg for ages above 6 months, values within the range of those in adults. Total ropivacaine clearance values per kg body weight increase from about 0.10 and 0.15 L/h/kg in the new born and the 1-month neonate to about 0.3-0.6 L/h/kg beyond the age of 6 months. Unbound ropivacaine volume of distribution per kg body weight increases from 22 and 26 L/kg in the new born and the 1-month neonate to 42-66 L/kg above 6 months. Total ropivacaine volume of distribution per kg body weight increases from 0.9 and 1.0 L/kg for new born and the 1-month neonate to 1.7-2.6 L/kg beyond the age of 6 months. The terminal half-life of ropivacaine is longer, 6 to 5 h in the new born and the 1-month neonate compared to about 3 h in older children. The terminal half-life of PPX is also longer, rom 43 and 26 h in the new born and the 1-month old neonate to about 15 h in older children.

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 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.

6. Pharmaceutical Particulars

6.1 List of Excipients

Sodium chloride
Sodium hydroxide/hydrochloric acid
Water for injection

6.2 Incompatibilities

Alkalisation can cause precipitation, as ropivacaine is hardly soluble at a pH above 6.0.

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Do not store above 30°C. Do not freeze.

6.5 Nature and Contents of Container

Each carton contains 10 x 20 mL Single dose vial.

6.6 Special Precautions for Disposal and other Handling

Ropivacaine Hydrochloride Solution for Injection or Infusion, USP contains no preservative and is intended for single-use only.

Remaining solution must be discarded.

7. Marketing Authorization Holder

Manufactured by:
Caplin Steriles Limited
Survey No 895 & 897 Gummidipoondi,
Tamil Nadu, 601201 India.

Code: TN/Drugs/TN00003457

Product Registration Holder:

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