SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ropivakain Sintetica 5 mg / ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 5 mg ropivacaine hydrochloride.
Each 10 ml ampoule contains 50 mg ropivacaine hydrochloride.

Excipient with known effect:
Each 10 ml ampoule contains 1.38 mmol (or 31.7 mg) of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Clear, colourless, sterile, isotonic, isobaric aqueous solution for injection with a pH of 4.0 to 6.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ropivakain Sintetica 5 mg/ml is indicated for

- intrathecal administration for surgical anaesthesia in adults
- Single peripheral nerve block in infants from 1 year and children up to and including 12 years of age for acute pain management (per and post-operative):

4.2 Posology and method of administration

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

Posology

Adults and children above 12 years of age
The following table is a guide to dosage for intrathecal block in adults. 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.

	Concentration mg/ml	**Volume ml**	**Dose mg**	**Onset minutes**	**Duration hours**
SURGICAL ANAESTHESIA					
Intrathecal Administration					

Surgery	5.0	3-5	15-25	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.

Paediatric population
Intrathecal administration has neither been investigated in infants, toddlers nor children.

Renal impairment
Normally there is no need to modify the dose in patients with impaired renal function when used for single dose or short-term treatment (see section 4.4. and 5.2).

Hepatic impairment
Ropivacaine hydrochloride 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 (see section 4.4. and 5.2).

Method of administration
Intrathecal administration for surgical anaesthesia

Careful aspiration before and during injection is recommended to prevent intravascular injection. An inadvertent intravascular injection may be recognised by a temporary increase in heart rate.

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

The intrathecal injection should be made after the subarachnoid space has been identified and clear cerebrospinal fluid (CFS) is seen to escape from the spinal needle, or is detected by aspiration.

Paediatric population
Infants and children aged 1-12 years

	Concentration	**Volume**	**Dose (mg/kg)**
ACUTE PAIN MANAGEMENT (per-and postoperative)			
Single injection for peripheral nerve block (e.g. ilioinguinal nerve block, brachial plexus block)	5.0 mg/ml	0.5 – 0.6 ml/kg	2.5 – 3.0 mg/kg

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.

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.

Ropivakain Sintetica 5 mg/mL is not approved for use in children <1 year; the use of ropivacaine in premature children has not been documented.

Method of administration
Intrathecal administration by injection.

Paediatric population
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.

Fractionation of the calculated local anaesthetic dose is recommended.With ultrasound techniques, often lower dosages may be necessary (see section 5.2).

High total plasma concentrations have been observed when ropivacaine 5 mg/mL was applied at doses of 3.5 mg/kg (0.7 mL/ kg) without the occurrence of systemic toxic events. It is recommended to use lower ropivacaine concentration for blocks where high volumes exceeding 3 mg/kg dose (0.6 mL/kg) are needed (e.g. fascia iliaca compartment block).

4.3 Contraindications

- Hypersensitivity to the active substance, to other local anaesthetics of the amide type, or to any of the excipients listed in section 6.1.
- General contraindications related to regional anaesthesia, regardless of the local anaesthetic used, should be taken into account
- Intravenous regional anaesthesia
- Obstetric paracervical anaesthesia
- Major nerve blocks are contraindicated in hypovolaemic patients

4.4 Special warnings and precautions for use

Regional anaesthetic procedures should always be performed in a properly equipped and staffed area. Equipment and medicinal products necessary for monitoring and emergency resuscitation should be immediately available.

Patients receiving major blocks should be in an optimal condition and have an intravenous line inserted before the blocking procedure.

The 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 undesirable effects, systemic toxicity and other complications (see section 4.8 and 4.9). After intrathecal administration, systemic toxicity is not expected to occur, due to the low dose administered. An excessive dose administered into the subarachnoid space may give rise to a total spinal block (see section 4.9).

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 drug class III (e.g. amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive.

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 intrathecal anaesthesia, regardless of the local anaesthetic used (see section 4.3).

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, however regional anaesthesia is frequently indicated in these patients.

Patients with renal and hepatic and renal impairment
Ropivacaine hydrochloride 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
Ropivakain Sintetica solution for injection 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 text books and/or in consultation with disease area experts.

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

Paediatric population
Intrathecal administration for use in infants, toddlers or children has not been documented.
The safety and efficacy of ropivacaine 5 mg/ml for peripheral nerve blocks in infants below 1 year have not been established.

Ropivakain Sintetica 5mg/ml is not approved for use in children < 1 year.
Neonates would need special attention due to immaturity of metabolic pathways. The larger variations in plasma concentration of ropivacaine observed in clinical trials in neonates suggest that there may be an increased risk of systemic toxicity in this age group.

Excipients with known effect:
This medicinal product contains 31.6 mg mg sodium per 10 ml, equivalent to 1.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Ropivacaine hydrochloride should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, e.g., certain antiarrhythmics, such as lidocaine and mexiletine, since the systemic toxic effects are additive. Simultaneous use of Ropivakain Sintetica with general anaesthetics or opioids may potentiate each other's (adverse) effects. Specific interaction studies with ropivacaine hydrochloride and anti-arrhythmic drugs class III (e.g., amiodarone) have not been performed, but caution is advised (see 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 hydrochloride 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 Ropivakain Sintetica, can interact with ropivacaine hydrochloride. Prolonged administration of ropivacaine hydrochloride should be avoided in patients concomitantly treated with strong CYP1A2 inhibitors, (see section 4.4).

In vivo the plasma clearance of ropivacaine hydrochloride 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 hydrochloride 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

Fertility
There are no data available concerning the fertility.

Pregnancy
Apart from epidural administration for obstetrical use, there are no adequate data on the use of ropivacaine hydrochloride in human pregnancy. Anyway, ropivacaine crosses the placenta (see section 5.2) and may lower the heart rate of the fetus, causing fetal bradycardia. Therefore, careful monitoring of the fetal heart rate is recommended. Experimental animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Depending on the dose, local anaesthetics may have a minor influence on mental function and coordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

The adverse reaction profile for Ropivakain Sintetica is similar to those for other long acting local anaesthetics of the amide type. Adverse reactions should be distinguished from the physiological effects of the nerve block itself e.g., hypotension and bradycardia during intrathecal anaesthesia, and events caused by needle puncture (e.g., spinal haematoma, postdural puncture headache, meningitis and epidural abscess).

The most frequently reported adverse reactions, nausea, vomiting and hypotension, are very frequent during anaesthesia and surgery in general and it is not possible to distinguish those caused by the clinical situation from those caused by the medicinal product or the block.

Total spinal block may occur with all local anaesthetics if an epidural dose is inadvertently administered intrathecally, or if a too large intrathecal dose is administered. Systemic and localised adverse reactions of ropivacaine hydrochloride usually occur because of excessive dosage, rapid absorption, or inadvertent intravascular injection. However, due to the low doses used for intrathecal anaesthesia, systemic toxic reactions are not expected.

The frequency of undesirable effects listed below is defined using the following convention:

Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

Psychiatric disorders:
Uncommon: Anxiety

Nervous system disorders:
Common: Headache*, paraesthesia, dizziness

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, Horner's syndrome

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,*]

Renal and urinary disorders:

Common:	Urinary retention*

General disorders and administration site conditions:

Common:	hyperthermia, chills
Uncommon:	Hypothermia*

Immune system disorders

Rare:	Allergic reactions (anaphylactic reactions, anaphylactic shock, angioneurotic oedema and urticaria)

Musculoskeletal and connective tissue

Common:	Back pain

* These reactions are more frequent than indicated after intrathecal administration.
**These symptoms usually occur because of inadvertent intravascular injection, overdose or rapid absorption (see section 4.9).
[a] Hypotension is less frequent in children (>1/100).
[b] Vomiting is more frequent in children (>1/10).

Class-related adverse 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.

Following epidural administration, cranial spread of local anaesthetic especially in pregnant women may occasionally result in Horner's syndrome characterised by miosis, ptosis, and anhidrosis. Spontaneous resolution occurs upon discontinuation of treatment.

Total spinal block
Total spinal block may occur 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 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 active substance, 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 auditory 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 an underlying neurological behaviour. Unconsciousness and tonic-clonic (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 active substance from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the medicinal product 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 hydrochloride 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 medicinal products 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 also section 4.4)

Treatment of acute systemic toxicity
See section 4.9.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 national reporting system listed in Appendix V.

4.9 Overdose

Symptoms of overdose

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. ”*Acute systemic toxicity*”, “*Central nervous system toxicity*” and “*Cardiovascular system toxicity*”).

After intrathecal administration, systemic toxicity is not expected to occur, due to the low dose administered. An excessive dose administered into the subarachnoid space may give rise to a total spinal block.

Treatment of overdose
If signs of acute systemic toxicity block 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, local, Amides, ATC code: N01BB09

Ropivacaine hydrochloride is a long-acting amide-type local anaesthetic with both anaesthetic and analgesic effects. At high doses ropivacaine hydrochloride 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 hydrochloride is the long duration of action. Onset and duration of the local anaesthetic efficacy are dependant upon the administration site and dose, but are not influenced by the presence of a vasoconstrictor (e.g., epinephrine). For details concerning the onset and duration of action of Ropivakain Sintetica (see section 4.2).

Healthy volunteers exposed to intravenous infusions tolerated ropivacaine hydrochloride well at low doses and with expected CNS symptoms at the maximum tolerated dose. The clinical experience with ropivacaine hydrochloride indicates a good margin of safety when adequately used in recommended doses.

5.2 Pharmacokinetic properties

Absorption and distribution
Ropivacaine hydrochloride 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 hydrochloride.

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

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

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

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

An increase in total plasma concentrations during continuous epidural 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.

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

Biotransformation and elimination

Ropivacaine hydrochloride 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 ropivacaine hydrochloride. 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 metabolite accounts for 1- 3%. Conjugated and unconjugated 3-hydroxy-ropivacaine shows only barely detectable concentrations in plasma.

Regarding metabolites a similar pattern has been found in paediatric patients above one year compared to adults.

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

Paediatric population

The pharmacokinetics of ropivacaine hydrochloride was characterised in a pooled population PK analysis on data in 192 children between 0 and 12 years. Unbound ropivacaine hydrochloride and PPX clearance and ropivacaine hydrochloride 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 hydrochloride clearance appears to be complete by the age of 3 years, that of PPX by the age of 1 year and unbound ropivacaine hydrochloride 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 hydrochloride clearance (Cl_u) for ages above 6 months has reached values within the range of those in adults. Total ropivacaine hydrochloride clearance (Cl) values displayed in the table are those not affected by the postoperative increase in AAG.

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

Age	BW[a]	Clu[b]	Vu[c]	Cl[d]	$t_{1/2}$[e]	$t_{1/2ppx}$[f]
Group	kg	(l/h/kg)	(l/kg)	(l/h/kg)	(h)	(h)
Newborn	3.27	2.40	21.86	0.096	6.3	43.3
1 m	4.29	3.60	25.94	0.143	5.0	25.7
6 m	7.85	8.03	41.71	0.320	3.6	14.5
1 y	10.15	11.32	52.60	0.451	3.2	13.6
4 y	16.69	15.91	65.24	0.633	2.8	15.1
10 y	32.19	13.94	65.57	0.555	3.3	17.8

[a] Median bodyweight for respective age from WHO database.

[b] Unbound ropivacaine hydrochloride clearance

[c] Ropivacaine hydrochloride unbound volume of distribution

[d] Total ropivacaine hydrochloride clearance

[e] Ropivacaine hydrochloride terminal half life

[f] PPX terminal half life

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

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

Age group	Dose	Cu_{max}[a]	t_{max}[b]	Cu_{max}[c]
	(mg/kg)	(mg/)	(h)	(mg/)
0-1 m	2.00	0.0582	2.00	0.05-0.08 (n=5)
1-6 m	2.00	0.0375	1.50	0.02-0.09 (n=18)
6-12 m	2.00	0.0283	1.00	0.01-0.05 (n=9)
1-10 y	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 hydrochloride 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 hydrochloride 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. In a study in children aged 1-12 years old (n=22) with a single ilioinguinal-iliohypogastric nerve block using 3mg/kg of ropivacaine 5 mg/L, absorption of ropivacaine was rapid with peak plasma concentrations attained 15-64 min after the start of injection. For total ropivacaine, the mean Cmax value was 1.5 ± 0.9 mg/L (with the highest value of 4.8 mg/L) with a mean elimination half-life of 2.0 ± 1.7 hours. The calculated unbound plasma concentration after 30 min was 0.05 ± 0.03 mg/L and the range at Cmax is 0.02 – 0.136 mg/L. 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 3mg/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.

In a published study comparing the pharmacokinetics of a single injection of ropivacaine 5mg/mL in ilioinguinal-iliohypogastric nerve block with ultrasound versus landmark guided technique, the ultrasound technique resulted in an increase of 45-56% of the Cmax and AUC levels, respectively, and a time reduction of 19% to reach the maximum plasma concentration. Hence, lower dosages can be applied with ultrasound techniques (see section 4.2).

5.3 Preclinical safety data

Based on conventional studies of safety pharmacology, single and repeated dose toxicity, reproduction toxicity, mutagenic potential and local toxicity, no hazards for humans were identified other than those which can be expected on the basis of the pharmacodynamic action of high doses of ropivacaine hydrochloride (e.g., CNS signs, including convulsions, and cardiotoxicity).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
In alkaline solutions precipitation may occur as ropivacaine hydrochloride shows poor solubility at pH > 6.0.

6.3 Shelf life

Shelf-life before opening
3 years

Shelf-life after 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.

6.4 Special precautions for storage

Do not freeze.
For storage conditions after opening the medicinal product, see section 6.3.

6.5 Nature and contents of container

Ropivakain Sintetica 5 mg/ml solution for injection
Polypropylene ampoules:
10 x 10ml - sterile ampoule, in plastic blister.

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

6.6 Special precautions for disposal and other handling

Handling
Ropivakain Sintetica products are preservative free and is intended for single use only. Discard any unused solution.

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.

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. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD/MM/YYYY}> <{DD month YYYY}>
<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

2025-12-17