Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naropin 5 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains ropivacaine hydrochloride monohydrate equivalent to 5 mg ropivacaine hydrochloride.

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

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection for intrathecal use.
Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Naropin 5 mg/ml is indicated for intrathecal administration for surgical anaesthesia.

4.2 Posology and method of administration

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

Posology
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.

	Conc. 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.

Children (<12 years)
Intrathecal administration has neither been investigated in infants, toddlers nor children.

Method of administration
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.

4.3 Contraindications

- Hypersensitivity to ropivacaine or to other local anaesthetics of the amide type.
- General contra-indications 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 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 Posology and method of administration)* and be appropriately trained and familiar with diagnosis and treatment of undesirable effects, systemic toxicity and other complications. 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 4.9 Overdose).*

Cardiovascular
Patients treated with anti-arrhythmic drugs class III (eg, 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 Contra-indications.*

Hypovolaemia
Patients with hypovolaemia due to any cause can develop sudden and severe hypotension during intrathecal 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 liver disease or severe renal dysfunction require special attention, however 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
Naropin® 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 textbooks and/or in consultation with disease area experts.

Excipients with recognised action/effect
This medicinal product contains maximum 3.5 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 concomitantly treated with strong CYP1A2 inhibitors, such as fluvoxamine and enoxacin, *(see 4.5 Interactions with other medicinal products and other forms of interaction).*

Paediatric patients
Intrathecal administration for use in infants, toddlers or children has not been documented.

4.5 Interaction with other medicinal products and other forms of interaction

Naropin should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, eg, certain antiarrhythmics, such as lidocaine and mexiletine, since the systemic toxic effects are additive. Simultaneous use of Naropin® with general anaesthetics or opioids may potentiate each other's (adverse) effects. Specific interaction studies with ropivacaine and anti-arrhythmic drugs class III (eg, amiodarone) have not been performed, but caution is advised *(see also section 4.4 Special warnings and precautions for use).*

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 Naropin, can interact with ropivacaine. Prolonged administration of Naropin should be avoided in patients concomitantly treated with strong CYP1A2 inhibitors, *(see 4.4 Special warnings and precautions for use).*

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.

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/fœtal development, parturition or postnatal development *(see 5.3 Preclinical safety data).*

Lactation
There is no data available concerning the excretion of ropivacaine into human 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 co-ordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

General
The adverse reaction profile for Naropin® 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 eg, hypotension and bradycardia during intrathecal anaesthesia, and events caused by needle puncture (eg, spinal hematoma, postdural puncture headache, meningitis and epidural abscess). Many of the most frequently reported adverse reactions, such as 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 Naropin® 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.

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

Very common (>1/10)	*Nervous System* Disorders: Headache *Cardiac Disorders:* Bradycardia *Vascular Disorders:* Hypotension *Gastrointestinal Disorders:* Nausea, Vomiting *Renal and Urinary Disorders:* Urinary retention
Common (>1/100, <1/10)	*Nervous System Disorders:* Paraesthesia, Dizziness, Hypoaesthesia *Vascular Disorders:* Syncope *Respiratory, thoracic and mediastinal disorders:* Dyspnoea *General Disorder and Administration Site Conditions:* Back pain, Hypothermia, Rigors
Rare (>1/10,000, <1/1,000)	*General Disorder and Administration Site Conditions:* Allergic reactions (anaphylactic reactions, angioneurotic oedema and urticaria)

Class-related adverse reactions
Neurological complications
Neuropathy and spinal cord dysfunction (eg, 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 too large an 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 vascularized areas. 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 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 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.

Treatment of acute systemic toxicity
See section 4.9 Overdose.

4.9 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 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

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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anesthetics, local, Amides
ATC code: N01B B09

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

The mechanism is a reversible reduction of the membrane permeability of the nerve fibre to sodium ions. Consequently the depolarisation velocity is decreased and the excitable threshold increased, resulting in a local blockade of nerve impulses.

The most characteristic property of ropivacaine is the long duration of action. Onset and duration of the local anaesthetic efficacy is dependant upon the administration site and dose, but are not influenced by the presence of a vasoconstrictor (eg, adrenaline).

For details concerning the onset and duration of action of Naropin, *see table under 4.2 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 ropivacaine indicates a good margin of safety when adequately used in recommended doses.

5.2 Pharmacokinetic properties

Ropivacaine has a chiral center 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.

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 min and 4 h in adults. The slow absorption is the rate-limiting factor in the elimination of ropivacaine, which explains why the apparent elimination half-life is longer after epidural than after intravenous administration.

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 intravenous 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 infusion has been observed, related to a postoperative increase of α_1-acid glycoprotein.

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

In children, aged between 1 and 12 years, ropivacaine pharmacokinetics after regional anaesthesia has been shown to be unrelated to age. In this group ropivacaine has a total plasma clearance in the order of 7.5 ml/min kg, an unbound plasma clearance of 0.15 l/min kg, a volume of distribution at steady state of 2.4 l/kg, an unbound fraction of 5% and a terminal half-life of 3 hours. Ropivacaine shows a biphasic absorption from the caudal space. The clearance related to body weight in this age group is similar to that in adults.

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 ropivacaine. The major metabolite is 3-hydroxy-ropivacaine, about 37% of which is excreted in the urine, mainly conjugated. Urinary excretion of 4-hydroxy-ropivacaine, the N-dealkylated metabolite and the 4-hydroxy-dealkylated metabolite accounts for 1-3%. Conjugated and unconjugated 3-hydroxy-ropivacaine shows only barely detectable concentrations in plasma.

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

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 (eg, CNS signs, including convulsions, and cardiotoxicity).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

10 ml polypropylene ampoules in sterile blisters of 5 and 10 ampoules.
Not all pack sizes may be marketed.

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

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Naropin 5 mg/ml is 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. A blistered container should be chosen when a sterile outside is required.

7 MARKETING AUTHORISATION HOLDER

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600 Capability Green
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UK

8 MARKETING AUTHORISATION NUMBER

PA 0970/047/009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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