Naropin 7.5 mg/ml solution for injection

1. NAME OF THE MEDICINAL PRODUCT
   Naropin® 7.5 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
   Naropin® 7.5 mg/ml:
   1 ml solution for injection contains ropivacaine hydrochloride monohydrate equivalent to 7.5 mg ropivacaine hydrochloride.

   1 ampoule of 10 ml or 20 ml solution for injection contains ropivacaine hydrochloride monohydrate equivalent to 75 mg and 150 mg ropivacaine hydrochloride respectively.

   For excipients, see section 6.1.

3. PHARMACEUTICAL FORM
   Solution for injection for perineural and epidural administration (10–20 ml).
   Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
   Naropin is indicated for:
   1. Surgical anaesthesia
      - Epidural blocks for surgery, including Caesarean section.
      - Major nerve blocks.
      - Field blocks.
   2. Acute pain management
      - Continuous epidural infusion or intermittent bolus administration during postoperative or labour pain.
      - Field blocks.

4.2 Posology and method of administration
   Naropin 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 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>
<thead>
<tr>
<th></th>
<th>Conc.</th>
<th>Volume</th>
<th>Dose</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/ml</td>
<td>ml</td>
<td>mg</td>
<td>minutes</td>
<td>hours</td>
</tr>
<tr>
<td><strong>Surgical anaesthesia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lumbar Epidural Administration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>15–20</td>
<td>150–200</td>
<td>10–20</td>
<td>4–6</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>7.5</td>
<td>15–20</td>
<td>113–150(1)</td>
<td>10–20</td>
<td>3–5</td>
</tr>
<tr>
<td><strong>Thoracic Epidural Administration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To establish block for postoperative pain relief</td>
<td>7.5</td>
<td>5–15 (depending on the level of injection)</td>
<td>38–113</td>
<td>10–20</td>
<td>n/a(2)</td>
</tr>
<tr>
<td><strong>Major Nerve Block</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial plexus block</td>
<td>7.5</td>
<td>30–40</td>
<td>225–300(3)</td>
<td>10–25</td>
<td>6–10</td>
</tr>
<tr>
<td>Field Block</td>
<td>7.5</td>
<td>1–30</td>
<td>7.5–225</td>
<td>1–15</td>
<td>2–6</td>
</tr>
<tr>
<td>(e.g. minor nerve blocks and infiltration)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute pain management</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lumbar Epidural Administration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolus</td>
<td>2</td>
<td>10–20</td>
<td>20–40</td>
<td>10–15</td>
<td>0.5–1.5</td>
</tr>
<tr>
<td>Intermittent injections (top up) (e.g. labour pain management)</td>
<td>2</td>
<td>10–15 (minimum interval 30 minutes)</td>
<td>20–30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous infusion e.g. labour pain Postoperative pain management</td>
<td>2</td>
<td>6–10 ml/h</td>
<td>12–20 mg/h</td>
<td>n/a(2)</td>
<td>n/a(2)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>6–14 ml/h</td>
<td>12–28 mg/h</td>
<td>n/a(2)</td>
<td>n/a(2)</td>
</tr>
<tr>
<td><strong>Thoracic Epidural Administration</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Continuous infusion (postoperative pain management)</td>
<td>2</td>
<td>6–14 ml/h</td>
<td>12–28 mg/h</td>
<td>n/a(2)</td>
<td>n/a(2)</td>
</tr>
<tr>
<td><strong>Field Block</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g. minor nerve blocks and infiltration)</td>
<td>2</td>
<td>1–100</td>
<td>2–200</td>
<td>1–5</td>
<td>2–6</td>
</tr>
<tr>
<td><strong>Peripheral nerve block</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(Femoral or interscalene block)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Continuous infusion or intermittent injections (e.g. postoperative pain management)</td>
<td>2</td>
<td>5–10 ml/h</td>
<td>10–20 mg/h</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

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.

* With regard to major nerve block, only for brachial plexus block a dose recommendation can be given. For other major nerve blocks lower doses may be required. However, there is presently no experience of specific dose recommendations for other blocks.
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 extra doses, in total an additional 50 mg, may be administered as needed.

(2) n/a = not applicable

The dose for a major nerve block must be adjusted according to site of administration and patient status. Interscalene and supraclavicular brachial plexus blocks may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used, (see section 4.4. Special warnings and special precautions for use).

In general, surgical anaesthesia (e.g. epidural administration) requires the use of the higher concentrations and doses. The Naropin 10 mg/ml formulation is recommended for epidural anaesthesia in which a complete motor block is essential for surgery. For analgesia (e.g. epidural administration for acute pain management) the lower concentrations and doses are recommended.

**Method of administration**

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) (Xylocaine® 2% with Adrenaline (epinephrine) 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.

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.

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

In brachial plexus block a single dose of 300 mg has been used in a limited number of patients and was 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 Naropin 7.5 mg/ml is induced via an epidural catheter. Analgesia is maintained with Naropin 2 mg/ml infusion. 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 Naropin 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 Naropin and fentanyl provided improved pain relief but caused opioid side effects. The combination of Naropin and fentanyl has been investigated only for Naropin 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 studies, femoral nerve block was established with 300 mg Naropin 7.5 mg/ml and interscalene block with 225 mg Naropin 7.5 mg/ml, respectively, before surgery. Analgesia was then maintained with Naropin 2 mg/ml. Infusion rates or intermittent injections of 10–20 mg per hour for 48 hours provided adequate analgesia and were well tolerated.

Concentrations above 7.5 mg/ml Naropin have not been documented for Caesarean section.

### 4.3 Contraindications

Hypersensitivity to ropivacaine 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.

### 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 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 side effects, systemic toxicity and other complications (see section 4.8 Undesirable effects and 4.9 Overdose) 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**

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 Naropin 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 blocks**

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.

**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 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**

Naropin® solution for injection and 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.

**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 concomitantly treated with strong CYP1A2 inhibitors, such as fluvoxamine and enoxacin, see section 4.5.

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, e.g. 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 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 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 Naropin. 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.

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/fetal development, parturition or postnatal development (see section 5.3 Preclinical safety data).

Lactation
There are no data available concerning the excretion of ropivacaine into human milk.

4.7 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.

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 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 of adverse drug reactions

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

<table>
<thead>
<tr>
<th>Very common (&gt;1/10)</th>
<th>Vascular Disorders</th>
<th>Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Common (&gt;1/100)</td>
<td>Nervous System Disorders</td>
<td>Headache, paraesthesia, dizziness</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Bradycardia, tachycardia</td>
<td></td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Urinary retention</td>
<td></td>
</tr>
<tr>
<td>General Disorder and Administration Site Conditions</td>
<td>Temperature elevation, rigor, back pain</td>
<td></td>
</tr>
<tr>
<td>Uncommon (&gt;1/1,000)</td>
<td>Psychiatric Disorders</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>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)⁴, Hypoaesthesia.</td>
<td></td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Syncope</td>
<td></td>
</tr>
</tbody>
</table>
Respiratory, Thoracic and Mediastinal Disorders
Dyspnoea

General Disorders and Administration Site Conditions
Hypothermia

Rare (>1/10,000) Cardiac Disorders
Cardiac arrest, cardiac arrhythmias

General Disorder and Administration Site Conditions
Allergic reactions (anaphylactic reactions, angioneurotic oedema and urticaria)

* 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 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.

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).

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, 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 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 Naropin, see table 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.

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 $C_{\text{max}}$ 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 iv administration. Ropivacaine has an intermediate hepatic extraction ratio of about 0.4. It is mainly bound to $\alpha_1$-acid glycoprotein in plasma with an unbound fraction of about 6%.

An increase in total plasma concentrations during continuous epidural infusion has been observed, related to a postoperative increase of $\alpha_1$-acid glycoprotein.

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

Ropivacaine readily crosses the placenta 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 and the 4-hydroxy-dealkylated accounts for 1–3%. Conjugated and unconjugated 3-hydroxy-ropivacaine shows only 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 (e.g. CNS signs, including convulsions, and cardiotoxicity).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
   Sodium chloride
   Hydrochloric acid
   Sodium hydroxide
   Water for injection

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

6.3 Shelf life
   3 years.
   Shelf life after first opening:
   From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2–8°C.

6.4 Special precautions for storage
   Do not store above 30°C. Do not freeze.
   For storage after opening, see section 6.3.

6.5 Nature and contents of container
   10 ml polypropylene ampoules (Polyamp) in packs of 5 and 10.
   10 ml polypropylene ampoules (Polyamp) in sterile blister packs of 5 and 10.
   20 ml polypropylene ampoules (Polyamp) in packs of 5 and 10.
   20 ml polypropylene ampoules (Polyamp) in sterile blister packs of 5 and 10.
   The polypropylene ampoules (Polyamp) are specially designed to fit Luer lock and Luer fit syringes.

6.6 Special precautions for disposal and other handling
   Naropin products are preservative-free and are intended for single use only. Discard any unused solution.
   The intact container must not be re-autoclaved. A blistered container should be chosen when a sterile outside is required.

7. MARKETING AUTHORISATION HOLDER
   AstraZeneca UK Ltd.,
   600 Capability Green,
   Luton, LU1 3LU, UK.

8. MARKETING AUTHORISATION NUMBER(S)
   PL 17901/0152

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   Date of first authorisation: 3rd October 1995
   Date of last renewal: 15th September 2005

10. DATE OF REVISION OF THE TEXT
    15th August 2008