1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

NAROPIN 2 mg/ml POLYAMP (injection)

NAROPIN 5 mg/ml POLYAMP (injection)

NAROPIN 7,5 mg/ml POLYAMP (injection)

NAROPIN 10 mg/ml POLYAMP (injection)

NAROPIN 2 mg/ml POLYBAG (infusion)

COMPOSITION

NAROPIN 2 mg/ml POLYAMP:

Each 1 ml of sterile solution for injection contains ropivacaine hydrochloride monohydrate equivalent to ropivacaine hydrochloride 2,0 mg.

NAROPIN 5 mg/ml POLYAMP:

Each 1 ml of sterile solution for injection contains ropivacaine hydrochloride monohydrate equivalent to ropivacaine hydrochloride 5,0 mg.

NAROPIN 7,5 mg/ml POLYAMP:

Each 1 ml of sterile solution for injection contains ropivacaine hydrochloride monohydrate equivalent to ropivacaine hydrochloride 7,5 mg.

NAROPIN 10 mg/ml POLYAMP:

Each 1 ml of sterile solution for injection contains ropivacaine hydrochloride monohydrate equivalent to ropivacaine hydrochloride 10,0 mg.

NAROPIN 2 mg/ml POLYBAG:

Each 1 ml of sterile solution for infusion contains ropivacaine hydrochloride monohydrate equivalent to ropivacaine hydrochloride 2,0 mg.

Excipients:

Sodium chloride, water for injection.

Sugar free

CATEGORY AND CLASS

A 4 Local anaesthetics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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 depend on the dose and site of administration, while presence of a vasoconstrictor (e.g. epinephrine (adrenaline)) has little, if any influence. Ropivacaine 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 the medicine reach the systemic circulation, symptoms and signs of toxicity may appear, emanating from the central nervous and cardiovascular systems. Indirect cardiovascular effects (hypotension, bradycardia) may occur after epidural administration, depending on the extent of the concomitant sympathetic block.

Pharmacokinetic properties

Ropivacaine is the S-(-)-enantiomer. 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 maximum plasma concentration is proportional to the dose. Ropivacaine shows complete and biphasic absorption from the epidural space, with half-lives of the 2 phases of the order of 14 minutes and 4 hours. The slow absorption is the rate-limiting factor in the elimination of ropivacaine. Ropivacaine has a mean total plasma clearance in the order of 440 ml/minute, an unbound plasma clearance of 8 litres/minute, a renal clearance of 1 ml/minute, a volume of distribution at steady state of 47 litres and a terminal half-life of 1,8 hours 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 and interscalene 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 in the liver, predominantly by aromatic hydroxylation to 3-hydroxy-ropivacaine mediated by cytochrome P4501A2 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. The metabolites have less activity than ropivacaine.

During epidural infusion, both PPX and 3-hydroxy-ropivacaine are the major metabolites excreted in the urine. A similar pattern of metabolites has been found in children above 1 year. There is no evidence of *in vivo* racemisation of ropivacaine.

Special populations

Paediatric patients

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 litre/min/kg, a volume of distribution at steady state of 2,4 litre/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.

INDICATIONS

NAROPIN is indicated for:

Adults: 2 mg/ml, 7,5 mg/ml, 10 mg/ml.

Surgical anaesthesia:

- Epidural block for surgery, including Caesarean section

- Minor nerve block and infiltration anaesthesia
- Major nerve block

Acute pain management:

- Continuous epidural infusion or intermittent bolus administration e.g. postoperative or labour pain
- Minor nerve block and infiltration analgesia
- Continuous peripheral nerve block infusion or intermittent injections, e.g. postoperative pain management

Children (1 to 12 years of age): 2 mg/ml and 5 mg/ml.

Acute pain management in paediatrics:

- Caudal epidural block
- Peripheral nerve block

for per and postoperative pain management.

CONTRAINDICATIONS

NAROPIN solutions are contraindicated in patients with known hypersensitivity to local anaesthetics of the amide-type.

Intravenous regional anaesthesia (Bier's block).

Obstetric paracervical anaesthesia.

Local anaesthetics are contraindicated for epidural and spinal anaesthesia in patients with uncorrected hypotension.

Local anaesthetic techniques must not be used when there is inflammation and/or sepsis in the region of the proposed injection and/or in the presence of septicaemia.

General contraindications related to epidural anaesthesia, regardless of the local anaesthetic used should be taken into account.

Until further experience has been documented NAROPIN is not recommended in children under the age of 1 year.

NAROPIN 7,5 mg/ml and 10 mg/ml should not be used in children below the age of 12 years as safety and efficacy have not been established.

WARNINGS AND SPECIAL PRECAUTIONS

Safe use of NAROPIN in lactating or pregnant women, other than those in labour, has not been established (see HUMAN REPRODUCTION).

NAROPIN should not be used for major nerve blocks unless the patients are in an optimal and haemodynamically stable condition.

NAROPIN should be administered in incremental doses, since NAROPIN should not be injected rapidly in large doses. It is not recommended for emergency situations, where a fast onset of surgical anaesthesia is necessary.

Local anaesthetics should only be employed by clinicians who are well versed in the diagnosis and management of dose related toxicity and other acute emergencies which might arise from the block to be employed, then only after insuring the immediate (without delay) availability of oxygen, other resuscitative medicines, cardiopulmonary resuscitative equipment, and the personnel resources needed for proper management of toxic

reactions and related emergencies. Delay in proper management of dose related toxicity,

under-ventilation from any cause and/or altered sensitivity may lead to the development of acidosis, cardiac arrest and possibly, death. Solutions of NAROPIN should not be used for the production of obstetrical paracervical block anaesthesia, retrobulbar block, or spinal anaesthesia (subarachnoid block) due to insufficient data to support such use.
Intravenous regional anaesthesia (Bier block) should not be performed due to a lack of clinical experience and a risk of attaining toxic blood levels of NAROPIN.

It is essential that aspiration for blood, or cerebrospinal fluid (where applicable), be done prior to injecting any local anaesthetic, both the original dose and all subsequent doses, to avoid intravascular or subarachnoid injection. However a negative aspiration does not ensure against an intravascular or subarachnoid injection.

NAROPIN should be used with caution in patients receiving local anaesthetics and agents structurally related to amide-type local anaesthetics, since the toxic effects of these medicines are additive (see INTERACTIONS).

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.

NAROPIN should not be given to patients with pre-existing abnormal neurological pathology, e.g. myasthenia gravis. Epidural, caudal and spinal anaesthesia should not be used in serious diseases of the CNS or of the spinal cord, e.g. meningitis, spinal fluid block, cranial or spinal haemorrhage, tumours, poliomyelitis, syphilis, tuberculosis or metastatic lesions of

the spinal cord.

WHEN ANY LOCAL ANAESTHETIC AGENT IS USED, RESUSCITATIVE EQUIPMENT AND MEDICINES, INCLUDING OXYGEN, SHOULD BE IMMEDIATELY AVAILABLE IN ORDER TO MANAGE POSSIBLE ADVERSE REACTIONS INVOLVING THE CARDIOVASCULAR, RESPIRATORY OR CENTRAL NERVOUS SYSTEMS. BECAUSE OF THE POSSIBLITY OF HYPOTENSION AND BRADYCARDIA FOLLOWING MAJOR BLOCKS, AN IV CANNULA SHOULD BE INSERTED BEFORE THE LOCAL ANAESTHETIC IS INJECTED. INJECTION SHOULD ALWAYS BE MADE SLOWLY WITH FREQUENT ASPIRATIONS TO AVOID INADVERTENT INTRAVASCULAR INJECTION, WHICH CAN PRODUCE TOXIC EFFECTS.

Patients receiving major blocks should be in an optimal and haemodynamically stable condition.

LOW MOLECULAR WEIGHT HEPARINS AND HEPARINOIDS (Spinal/Epidural Haematomas) - When neuraxial anaesthesia (epidural/spinal anaesthesia) is employed, patients anti-coagulated or scheduled to be anti-coagulated with low molecular weight heparins or heparinoids are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters, traumatic or repeated epidural/spinal puncture, and the concomitant use of medicines affecting haemostasis such as NSAIDs, platelet inhibitors or other anticoagulants. Patients should be frequently monitored for signs and symptoms of neurological impairment.

The safety and efficacy of NAROPIN depends on proper dosage, correct technique and

adequate precautions. Standard textbooks should be consulted regarding specific techniques and precautions for various regional anaesthetic procedures.

The lowest dosage that results in efficacious anaesthesia should be used (see DOSAGE AND DIRECTIONS FOR USE).
NAROPIN should be used with caution in patients with known medicinal product sensitivities.

Careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness should be accomplished after each NAROPIN injection. It should be kept in mind that at such times restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of CNS toxicity.

Regional anaesthetic procedures with NAROPIN should always be performed in a properly equipped and staffed area. Equipment and medicines necessary for monitoring and emergency resuscitation should be immediately available. Patients receiving major blocks should be in an optimal condition and have an IV line inserted before the blocking procedure. The clinician responsible should take the necessary precautions to avoid intravascular injection and be appropriately trained and familiar with the diagnosis and treatment of side effects, systemic toxicity and other complications.

Certain local anaesthetic procedures such as injection with NAROPIN in the head and neck region, including retrobulbar, dental and stellate ganglion blocks, may be associated with a higher frequency of serious adverse reactions. The side effects may be similar to the systemic toxicity seen with unintentional intra-vascular injections of larger doses.

Elderly, young and debilitated patients, including those with partial or complete heart conduction block, advanced liver disease or severe renal dysfunction should be given

reduced doses commensurate with their age and physical condition.

Patients treated with antidysrhythmic medicines class III (e.g. amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive (see INTERACTIONS).

There have been rare reports of cardiac arrest during the use NAROPIN for epidural anaesthesia or peripheral nerve blockade, of 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.

NAROPIN is metabolised in the liver. It should therefore be used with caution in patients with severe liver disease and 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 The risk should also be considered in patients suffering from malnutrition or patients with hypovolaemia.

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

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

necessary.

Prolonged administration of NAROPIN should be avoided in patients treated with strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin (see INTERACTIONS).

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.

Effects on ability to drive and use machines

Besides the direct anaesthetic effect, NAROPIN may have an effect on mental function and co-ordination even in the absence of overt central nervous system toxicity and may temporarily impair locomotion and alertness.

INTERACTIONS

NAROPIN should be used with caution in patients receiving other local anaesthetic or agents structurally related to amide-type local anaesthetics, e.g. certain antidysrhythmics, such as lidocaine and mexiletin, since the systemic toxic effects are additive.

Specific interaction studies with NAROPIN and antidysrhythmic medicines class III (e.g. amiodarone) have not been performed, but caution is advised.

In healthy volunteers, ropivacaine clearance was reduced by up to 77 % during co-administration of fluvoxamine, a potent competitive inhibitor of P4501A2. 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 NAROPIN can

cause a metabolic interaction leading to an increased ropivacaine plasma concentration. Prolonged administration of NAROPIN should therefore be avoided in patients treated with strong inhibitors of CYP1A2 such as fluvoxamine and enoxacin.

HUMAN REPRODUCTION

Safe use of NAROPIN in lactating or pregnant women, other than those in labour, has not been established. Foetal bradycardia frequently follows paracervical block with some amide-type local anaesthetics (such as NAROPIN) and may be associated with foetal acidosis. Added risk appears to be present in prematurity, toxaemia of pregnancy and foetal distress. Until further clinical experience in pregnancy is gained, the use of NAROPIN is not recommended (see WARNINGS AND SPECIAL PRECAUTIONS).

DOSAGE AND DIRECTIONS FOR USE

NAROPIN should only be used by or under the supervision of clinicians experienced in regional anaesthesia. NAROPIN should not be administered intravenously. 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.

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 to 50 mg/min, while closely observing the patient's vital functions and maintaining verbal contact. When an epidural dose is to be injected, a standard test dose technique is advised. 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.

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 is generally recommended.

NAROPIN is not recommended for children under the age of 1 year and in patients under 60 kg for major nerve block anaesthesia, as safety and efficacy have not been established.

Dosage recommendations for NAROPIN in adults:

	Conc. mg/ml	Volume ml	Dose mg	Onset minutes	Duration hours
SURGICAL ANAESTHESIA					
Lumbar Epidural Administration					
Surgery	7,5	15 to 25	113 to 188	10 to 20	3 to 5
	10,0	15 to 20	150 to 200	10 to 20	4 to 6
Lumbar Epidural Administration					
Caesarean Section	7,5	15 to 20	113 to 150	10 to 20	3 to 5
Thoracic Epidural Administration					
To establish block for postoperative pain relief	7,5	5 to 15 Depending on level of injection	38 to 113	10 to 20	n/a
Minor Nerve Block and infiltration anaesthesia					

(e.g. minor nerve blocks and infiltration)	7,5	1 to 30	7,5 to 225	1 to 15	2 to 6
Major Nerve Block					
(e.g. brachial plexus)	7,5	10 to 40	75 to 300*	10 to 25	6 to 10
ACUTE PAIN MANAGEMENT					
Lumbar Epidural Administration					
Bolus	2,0	10 to 20	20 to 40	10 to 15	0,5 to 1,5
Intermittent injections (top-up) (e.g. labour pain management)	2,0	10 to 15 (minimum interval 30 minutes)	20 to 30		
Lumbar Epidural Administration					
Continuous infusion	2,0	6 to 10 ml/h	12 to 20 mg/h	n/a	n/a
(e.g. Labour pain Postoperative pain management)	2,0	6 to 14 ml/h	12 to 28 mg/h	n/a	n/a
ACUTE PAIN MANAGEMENT					
Thoracic Epidural Administration					
Continuous infusion (e.g. postoperative pain management)	2,0	6 to 14 ml/h	12 to 28 mg/h	n/a	n/a
Minor Nerve Block and infiltration analgesia					
(e.g. minor nerve blocks and infiltration)	2,0	1 to 100	2 to 200	1 to 5	2 to 6

Peripheral Nerve Block					
(Femoral or interscalene block) Continuous infusion or intermittent injections (e.g. postoperative pain management)	2,0	5 to 10 ml/h	10 to 20 mg/h	n/a	n/a

*NAROPIN plasma concentrations may approach the threshold for central nervous toxicity after administration of 300 mg of ropivacaine for brachial plexus block in adult patients of 60 kg or more. Data on patients under 60 kg is not available. Caution should be exercised when using the 300 mg dose.

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.

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 reflect the expected average dose range needed. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements. When prolonged epidural 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 800 mg NAROPIN 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.

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 (preoperatively placed). Analgesia is maintained with NAROPIN 2 mg/ml infusion.

Clinical studies have demonstrated that infusion rates of 6 to 14 ml (12 mg to 28 mg) per hour provide adequate analgesia with only slight and non-progressive motor block in most cases of moderate to severe postoperative pain.

For caesarean section, neither intrathecal administration nor the use of the NAROPIN concentration 10 mg/ml for epidural administration, have been documented.

Pediatrics:

Dosage recommendations for pediatric patients 1 to 12 years of age:

ACUTE PAIN MANAGEMENT (peri- and postoperative)	Conc. mg/ml	Volume ml/kg	Dose mg/kg
Single caudal epidural block administration Blocks below T12, in children with a body weight up to 25 kg	2,0	1	2
Peripheral nerve block (e.g. ilioinguinal nerve block)	5,0	0,6	3

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

requirements.

A 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. In children above 4 years of age, doses up to 3 mg/kg have been studied. However, this concentration is associated with a higher incidence of motor block. The volume of the caudal epidural injection may be adjusted to achieve a different distribution of sensory block, as recommended in standard textbooks.

For ilioinguinal block, a single injection of ropivacaine 5 mg/ml produces effective analgesia when a dose of 3 mg/kg in a volume of 0,6 ml/kg is used.

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

Until further experience has been gained, NAROPIN cannot be recommended for use in children below the age of 1 year. Concentrations above 5 mg/ml have not been documented for children.

NOTE:
The products contain no preservatives and are intended for single use only. Any solution remaining from an opened container should be discarded.

Alkalisation may lead to precipitation since ropivacaine is poorly soluble above pH 6,0.

NAROPIN solution for infusion in plastic infusion bags (POLYBAG) is chemically and physically compatible with the following medicines:

Concentration of NAROPIN: 1 to 2 mg/ml	
Additive	Concentration
Fentanyl citrate	1,0 to 10,0 microgram/ml
Sufentanil citrate	0,4 to 4,0 microgram/ml
Morphine sulphate	20,0 to 100,0 microgram/ml
Clonidine hydrochloride	5,0 to 50,0 microgram/ml

The mixtures are chemically and physically stable for 30 days at up to 30 °C. From a microbiological point of view, the mixtures should be used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

SIDE EFFECTS

The effects of systemic overdose and unintentional intravascular injections can be serious (see KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT).

In children the most commonly reported adverse events (> 1 %) are vomiting, nausea and pruritus. NAROPIN may cause acute toxic effects after high doses or if very rapidly rising blood levels occur due to accidental intravascular injection or overdose. One case of convulsions has been observed after an unintended intravascular injection at an attempted brachial plexus block with 200 mg.

Side effects reported after use of NAROPIN include physiological effects of the nerve block itself, e.g. hypotension, bradycardia and urinary retention after epidural and intrathecal block, and events caused directly by needle puncture (e.g. spinal haematoma, postdural puncture headache), or indirectly by introduction of micro-organisms (e.g. meningitis and epidural

abscess).

The table of adverse reactions includes reactions caused by the medicine per se and also frequently associated physiological side effects.

The percentage of patients that can be expected to experience adverse reactions varies with the route of administration of NAROPIN. Systemic adverse reactions of NAROPIN usually occur because of inadvertent intravascular injection, excessive dosage or rapid absorption.

Table of adverse reactions (pooled data from all types of blocks):		
Very common: (≥ 1/10)	Vascular disorders: Gastrointestinal disorders:	Hypotension Nausea
Common: (≥ 1/100)	Nervous system disorders: Cardiac disorders: Vascular disorders: Gastrointestinal disorders: Renal and urinary disorders: General disorders and administration site conditions:	Paraesthesia, dizziness, headache Bradycardia, tachycardia Hypertension Vomiting Urinary retention Temperature elevation, rigor, back pain
Uncommon: (≥ 1/1 000)	Psychiatric disorders: Nervous system disorders:	Anxiety 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
	Vascular disorders:	Syncope
	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, angio-oedema,angioneurotic oedema and urticaria)

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

Class-related adverse reactions:

This section includes 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 damage), have been associated with epidural anaesthesia.

Total spinal block:

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Accidental intravascular injections of NAROPIN may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, systemic toxicity appears later (15 to 60 minutes after injection) due to the slower increase in local anaesthetic blood concentration (see SIDE EFFECTS and WARNINGS AND SPECIAL PRECAUTIONS).

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.

Central nervous system 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 or tremors are more serious and 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 following convulsions due to the increased muscular activity, together with the interference with respiration and possible loss of functional airways. In severe cases apnoea may occur. Acidosis hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

Recovery is due to redistribution of NAROPIN from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the medicine have been injected.

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, dysrhythmia and even 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.

Treatment of acute systemic toxicity:

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

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.

IDENTIFICATION

NAROPIN 2; 5; 7,5; 10 mg/ml POLYAMP:

A sterile, isotonic, isobaric, clear and colourless solution for injection designed to fit luer lock and luer fit.

NAROPIN 2 mg/ml POLYBAG:

A sterile isotonic, isobaric, clear and colourless solution for infusion.

PRESENTATION

NAROPIN 2; 5; 7,5; 10 mg/ml POLYAMP:

Polypropylene ampoules (POLYAMP) available in pack sizes of 10 ml and 20 ml, either blister packed into transparent polypropylene blisters, or single.

The blisters are packed into a cardboard unit carton with a leaflet.

NAROPIN 2 mg/ml POLYBAG:

NAROPIN 2 mg/ml Polybags are available in polypropylene infusion bags of 125 ml (containing 100 ml of solution) and 250 ml (containing 200 ml of solution). The polybag contains a chlorobutyl rubber stopper.

The polybag is covered with a polypropylene blister, with an outer cover of autoclave paper.

Not all packs or pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 30 °C.

Avoid freezing.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

NAROPIN 2 mg/ml POLYAMP: 31/4/0124

NAROPIN 2 mg/ml POLYBAG: 31/4/0125

NAROPIN 5 mg/ml POLYAMP: 35/4/0409

NAROPIN 7,5 mg/ml POLYAMP: 31/4/0126

NAROPIN 10 mg/ml POLYAMP: 31/4/0127

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharmacare Limited

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Date of registration: 15 April 1997

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Namibia:	NS2
2 mg/ml POLYBAG	04/4/1815
7,5 mg/ml POLYAMP	04/4/1816
10 mg/ml POLYAMP	04/4/1817

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