NAROPIN® with FENTANYL PRODUCT INFORMATION
(ropivacaine hydrochloride with fentanyl citrate)

NOT FOR INTRAVENOUS ADMINISTRATION UNDER ANY CIRCUMSTANCES

NAME OF THE MEDICINE

The active ingredients in Naropin with fentanyl are ropivacaine hydrochloride and fentanyl citrate.

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\begin{align*}
\text{ropivacaine hydrochloride} & \quad \text{fentanyl citrate} \\
\text{MW 328.89} & \quad \text{MW 528.61}
\end{align*}
\]

The CAS number for the free base ropivacaine is 84057-95-4. The CAS number for fentanyl citrate is 990-73-8. The chemical formula of ropivacaine hydrochloride is \(\text{C}_{17}\text{H}_{26}\text{N}_{2}\text{O}.\text{HCl}.\text{H}_{2}\text{O}\). The chemical formula for fentanyl citrate is \(\text{C}_{22}\text{H}_{28}\text{N}_{2}\text{O}, \text{C}_{6}\text{H}_{8}\text{O}_{7}\).

DESCRIPTION

The chemical name for ropivacaine hydrochloride is (S)-(\text{-})-propyl-piperidine-2-carboxylic acid (2,6-dimethyl-phenyl)-amide hydrochloride monohydrate. It is a white crystalline powder and has a water solubility of about 50 mg/mL. Ropivacaine hydrochloride was developed as the pure S-(\text{-})-isomer and has an enantiomeric purity of > 99%. It has a pKa of 8.1 (at 25 °C). The Australian approved name is ropivacaine hydrochloride.

The chemical name for fentanyl citrate is \(\text{N-}(1\text{-phenethyl-4-piperidyl}) \text{ propionanilide citrate}\). It is a white crystalline powder sparingly soluble in water.

Naropin with fentanyl solution is available in Polybag® in two strengths; ropivacaine 2 mg/mL with fentanyl 2 \(\mu\)g/mL and ropivacaine 2 mg/mL with fentanyl 4 \(\mu\)g/mL. The injection solution also contains sodium chloride and water for injections. Naropin with fentanyl is a sterile, isotonic solution with nominal osmolality of 288 mOsmol/kg. The pH of the solution is adjusted with sodium hydroxide or hydrochloric acid to remain between 4.0-6.0 during the approved shelf-life.
Naropin with fentanyl injection solutions do not contain a preservative. Each Polybag is intended for single use only, not exceeding 24 hours. Any solution remaining from an opened Polybag should be discarded.

PHARMACOLOGY

Ropivacaine
Ropivacaine has both anaesthetic and analgesic effects. At higher doses it produces surgical anaesthesia with motor block, while at lower doses it produces a sensory block including analgesia with little motor block.

The duration and intensity of ropivacaine sensory block is not improved by the addition of adrenaline.

Ropivacaine, like other local anaesthetics, causes reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the cell membrane of the nerve fibres. It is the first long acting amide local anaesthetic developed as a pure enantiomer. There is no evidence of in vivo racemisation of ropivacaine.

Fentanyl
Fentanyl is an opioid analgesic with pharmacologic effects similar to morphine and pethidine. It is 50 to 100 times more potent than morphine on a weight basis. Fentanyl citrate 157 µg is approximately equivalent to 100 µg of fentanyl. A dose of 100 µg fentanyl is approximately equivalent in analgesic activity to 10 mg of morphine or 75 mg of pethidine. The principal actions of therapeutic value are analgesia and sedation.

Pharmacodynamics

Ropivacaine
The local anaesthetic effect of ropivacaine and its R-(+) enantiomer was evaluated for sciatic block, spinal anaesthesia and infiltration anaesthesia over a wide concentration range (0.25 - 1.0%) in a number of animal species and a concentration-(dose-) response relationship was ascertained. These studies supported the selection of the enantiomerically pure drug ropivacaine and are consistent with the observations with other local anaesthetics that the S-(-) form is less toxic and/or has a longer duration of action than the R-(+) form.

In vitro testing of ropivacaine conduction anaesthesia indicate that ropivacaine is comparable to, or slightly more potent than, bupivacaine in blocking sensory fibres and is less active in blocking motor fibres.

The anaesthetic effects of ropivacaine were evaluated in peripheral (sciatic nerve and brachial plexus) and central (spinal and epidural) neural blocks, as well as in infiltration and topical anaesthesia in a large number of studies using multiple animal species including mouse, rat, guinea-pig, dog, sheep and Rhesus monkey.
For central neural blockade, for all species studied, it appeared that onset times of epidural anaesthesia with ropivacaine and bupivacaine were similar. The concentration required to consistently produce complete motor blockade with epidural block appeared to be 0.75 - 1.0% for ropivacaine. Duration of sensory anaesthesia appeared to be comparable for equal concentrations of ropivacaine and bupivacaine.

For analgesia, the potency of ropivacaine is similar to that of bupivacaine. For motor block, the potency was found to be around 80% of bupivacaine.

Cardiovascular effects measured in vivo in animal studies showed that ropivacaine is consistently well tolerated and that ropivacaine is less likely than bupivacaine to produce ventricular arrhythmias. Resuscitative measures were highly successful in dogs given large overdoses (9.8 mg/kg given intravenously) of ropivacaine. In most preclinical studies of the cardiovascular effects, comparisons were also made with lignocaine. In general all results were consistent with the observation that a given dose of lignocaine was less toxic than an equivalent dose of ropivacaine or bupivacaine.

Ropivacaine and bupivacaine are equipotent in producing seizures in rats and dogs. In both pregnant and non-pregnant sheep, ropivacaine was less toxic than bupivacaine.

Comparisons with the short acting local anaesthetic lignocaine shows that the doses needed to produce seizures are 2 (in sheep) to 4 (in rats and dogs) times the dose of ropivacaine. In studies in sheep ropivacaine appears to have less central nervous system and cardiovascular toxicity than bupivacaine, and pregnancy does not appear to enhance sensitivity in either the central nervous system or in cardiac membranes as has been reported in some studies with bupivacaine.

In vitro heart studies indicate that the effects of ropivacaine on conduction and contractility are less compared to bupivacaine. The risk of ventricular tachycardia is less with ropivacaine than bupivacaine. Atrial and ventricular pacing were more successful during exposure to high concentrations of ropivacaine compared to bupivacaine. The in vitro electrophysiological studies are consistent with the findings in the in vitro heart preparation.

In man, ropivacaine is less toxic regarding the CNS and cardiovascular systems than bupivacaine. In two tolerability studies in volunteers given i.v. infusions, CNS symptoms appeared at higher doses and higher free plasma concentrations of ropivacaine compared to bupivacaine. The ropivacaine dose-response and concentration-response curves for CNS symptoms, e.g. muscular twitching, dysarthria, were consistently shifted to the right compared with those of bupivacaine. A threshold for CNS toxicity was apparent at mean free plasma concentrations in the order of 0.6 mg/L ropivacaine and 0.3 mg/L bupivacaine. Ropivacaine caused a smaller increase in the QRS width and less pronounced reduction in diastolic and systolic function of the left ventricle as compared to bupivacaine.

Factors which may increase the relative systemic toxicity of local anaesthetics are acidosis and severe hepatic dysfunction.
Ropivacaine, like bupivacaine and other local anaesthetics, produces vasoconstriction at lower concentrations and vasodilation at higher concentrations. These findings appear to be consistent both in vivo and in vitro.

Pharmacodynamic drug interactions between ropivacaine and other agents used in conjunction with epidural anaesthesia are similar to those seen with bupivacaine and lignocaine. These probably depend more on the physiological effects of the block, such as hypotension and bradycardia, than on circulating blood levels of the local anaesthetic.

**Fentanyl**

Fentanyl is an opioid analgesic. The principal actions of therapeutic value are analgesia and sedation. When given epidurally, opioids produce selective analgesia by blocking opioid receptors in the dorsal horn. Opioids may produce dose related respiratory depression. Alterations in respiratory rate and alveolar ventilation may last longer than the analgesic effect. As the dose of opioid is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnoea.

Histamine assays and skin wheal testing in man indicate that clinically significant histamine release rarely occurs with fentanyl. Fentanyl appears to have less emetic activity than either morphine or pethidine. Fentanyl preserves cardiac stability and blunts stress-related hormonal changes at higher doses. Fentanyl produces minimal cortical depression and may act by filling receptor sites located in the thalamus, midbrain and spinal cord.

A specific opioid antagonist (e.g. nalorphine) produces reversal of respiratory, cardiovascular, miotic and motor incoordination effects and also produces reversal of analgesia, euphoria and sedation. Cholinergic effects such as bradycardia are reversed by atropine.

**Pharmacokinetics**

**Ropivacaine**

The plasma concentration of ropivacaine depends upon the dose, the route of administration and the vascularity of the injection site. Ropivacaine has 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 two phases in the order of 14 minutes and 4 hours. The slow absorption is the rate limiting factor in the elimination of ropivacaine, which explains why the apparent elimination half-life is longer after epidural than after intravenous administration.
The pharmacokinetic profile of ropivacaine following experimental i.v. administration is summarized below:

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Plasma clearance</td>
<td>440 mL/min</td>
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<tr>
<td>Unbound plasma clearance</td>
<td>8 L/min</td>
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<tr>
<td>Renal clearance</td>
<td>1 mL/min</td>
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<tr>
<td>Volume of distribution at steady-state</td>
<td>47 L</td>
</tr>
<tr>
<td>Unbound volume of distribution at steady-state</td>
<td>819 L</td>
</tr>
<tr>
<td>Terminal half-life</td>
<td>1.8 h</td>
</tr>
<tr>
<td>Unbound fraction</td>
<td>0.06</td>
</tr>
<tr>
<td>Hepatic extraction ratio</td>
<td>0.4</td>
</tr>
<tr>
<td>Major metabolite</td>
<td>3-OH-ropivacaine</td>
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</table>

Ropivacaine is mainly bound to α1-acid glycoprotein in plasma with an unbound pharmacologically active fraction of about 6%. An increase in total plasma concentrations during continuous postoperative epidural infusion has been observed. This increase is related to a postoperative increase of α1-acid glycoprotein. Variations in unbound concentration of ropivacaine have been much less than in total plasma concentration.

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% is unchanged drug. Approximately 9% is excreted in faeces.

Both the dealkylation (N-depropylated or PPX) and the hydroxylation pathways in the metabolism of ropivacaine are detoxification reactions. PPX is considered to have no or very little pharmacological activity. The hydroxylated metabolites of ropivacaine have some local anaesthetic activity (ropivacaine > 3-hydroxy-ropivacaine >> 4-hydroxy-ropivacaine). The hydroxylated metabolites are rapidly conjugated in human plasma and are very unlikely to have any pharmacological or toxicological activities.

The major metabolite is 3-hydroxy-ropivacaine. This metabolite accounts for about 37% of urinary excretion, mainly as a glucuronide conjugate. The only metabolite which reaches detectable concentrations in plasma is 3-hydroxy-ropivacaine (conjugated and un conjugated). Urinary excretion of 4-hydroxy-ropivacaine, the N-dealkylated metabolite and the 4-hydroxy-dealkylated metabolite accounts for 1 - 3% of a given dose.

The NADPH-dependent metabolism of ropivacaine to 3-hydroxy-ropivacaine is catalysed by CYP1A2. The formation of minor metabolites in vivo is catalysed by CYP3A4. The apparent Km (affinity constant) for 3-hydroxy-ropivacaine is 16 µM and about 400 µM for the other metabolites. Of the two members in the CYP1A family, CYP1A1 is expressed only after exposure to inducers, while CYP1A2 accounts for about 10% of total P450 in the liver.

Impaired renal function has little or no influence on ropivacaine pharmacokinetics. The renal clearance of PPX is significantly correlated with creatinine clearance. A lack of correlation between total exposure, expressed as AUC, with creatinine
clearance indicates that the total clearance of PPX includes a non-renal elimination in addition to renal excretion. Some patients with impaired renal function may show an increased exposure to PPX resulting from a low non renal clearance. The potential for toxicity in these patients is dependent on the total dose, dose route and duration of exposure to ropivacaine.

**Fentanyl**  
The pharmacokinetics of fentanyl can be described by a three-compartment model, with a distribution time of 1.7 minutes, redistribution of 13 minutes and a terminal elimination half-life of 219 minutes. The volume of distribution for fentanyl is 4 L/kg. Fentanyl accumulates in skeletal muscle and fat, and is released slowly into the blood.

Fentanyl plasma protein binding capacity increases with increasing ionisation of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system.

Fentanyl is primarily transformed in the liver, catalysed by CYP3A4 and demonstrates a high first pass clearance with approximately 75% of an intravenous dose excreted in urine, primarily as inactive metabolites with less than 10% representing the unchanged drug. Approximately 9% of the dose is recovered in the faeces, primarily as metabolites.

**INDICATIONS**

For the management of post-operative pain by epidural infusion for up to 72 hours.

**CONTRAINDICATIONS**

1. Allergy or hypersensitivity to amide type local anaesthetics, fentanyl or other ingredients contained in Naropin with fentanyl solution (see DESCRIPTION).

2. Intravenous administration.

3. Epidural anaesthesia is contraindicated in patients with uncorrected hypotension.

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

5. As with all ropivacaine solutions, ropivacaine is contraindicated in obstetric paracervical block, intravenous regional anaesthesia (Bier’s block) and all intravenous infusions.

6. Fentanyl should not be administered to patients who are taking or have taken a mono-amine oxidase inhibitor (including selegiline) within the previous fourteen days.
7. Fentanyl should not be used in patients susceptible to respiratory depression, or in patients whom respiratory reserve is significantly depleted (e.g. comatose patients who may have head injuries or a brain tumour).

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

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

PRECAUTIONS

1. WHEN NAROPIN WITH FENTANYL IS USED, RESUSCITATIVE EQUIPMENT AND DRUGS, INCLUDING OXYGEN AND AN OPIOID ANTAGONIST, SHOULD BE IMMEDIATELY AVAILABLE IN ORDER TO MANAGE POSSIBLE ADVERSE REACTIONS INVOLVING THE CARDIOVASCULAR, RESPIRATORY OR CENTRAL NERVOUS SYSTEMS. BECAUSE OF THE POSSIBILITY OF HYPOTENSION AND BRADYCARDIA FOLLOWING MAJOR BLOCKS, AN IV CANNULA SHOULD BE INSERTED BEFORE THE SOLUTION IS INJECTED.

2. INJECTION SHOULD ALWAYS BE MADE SLOWLY WITH FREQUENT ASPIRATIONS TO AVOID INADVERTENT INTRAVASCULAR INJECTION WHICH CAN PRODUCE TOXIC EFFECTS.

3. ALTHOUGH INTRA-ARTICULAR CONTINUOUS INFUSIONS OF LOCAL ANAESTHETICS FOLLOWING ARTHROSCOPIC AND OTHER SURGICAL PROCEDURES IS AN UNAPPROVED USE, THERE HAVE BEEN POST-MARKETING REPORTS OF CHONDROLYSIS IN PATIENTS RECEIVING SUCH INFUSIONS. THE MAJORITY OF REPORTED CASES OF CHONDROLYSIS HAVE INVOLVED THE SHOULDER JOINT; CASES OF GLENO-HUMERAL CHONDROLYSIS HAVE BEEN DESCRIBED IN PAEDIATRIC AND ADULT PATIENTS FOLLOWING INTRA-ARTICULAR CONTINUOUS INFUSIONS OF LOCAL ANAESTHETICS WITH AND WITHOUT ADRENALINE FOR PERIODS OF 48 TO 72 HOURS. THERE IS INSUFFICIENT INFORMATION TO DETERMINE WHETHER SHORTER INFUSION PERIODS ARE NOT ASSOCIATED WITH THESE FINDINGS. THE TIME OF ONSET OF SYMPTOMS, SUCH AS JOINT PAIN, STIFFNESS AND LOSS OF MOTION CAN BE VARIABLE, BUT MAY BEGIN AS EARLY AS THE SECOND MONTH AFTER SURGERY. CURRENTLY, THERE IS NO EFFECTIVE TREATMENT FOR CHONDROLYSIS; PATIENTS WHO EXPERIENCED CHONDROLYSIS HAVE REQUIRED ADDITIONAL DIAGNOSTIC AND THERAPEUTIC PROCEDURES AND SOME REQUIRED ARTHROPLASTY OR SHOULDER REPLACEMENT. THEREFORE, NAROPIN WITH FENTANYL SHOULD NOT BE USED FOR POST-OPERATIVE INTRA-ARTICULAR CONTINUOUS INFUSION.

4. 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 drugs affecting haemostasis such as NSAIDs, platelet inhibitors or other anticoagulants. Patients should be frequently monitored for signs and symptoms of neurological impairment.

5. The safety and efficacy of Naropin with fentanyl depends on proper dosage, correct technique and adequate precautions. Standard textbooks should be consulted regarding specific techniques and precautions for epidural analgesia.

6. The lowest dosage that results in efficacious analgesia should be used (see DOSAGE AND ADMINISTRATION).

   Elderly, young or 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.

7. Ropivacaine is eliminated primarily by hepatic metabolism and changes in hepatic function may have significant consequences. Ropivacaine has an intermediate to low clearance, which depends on its unbound fraction and intrinsic metabolic clearance. Naropin with fentanyl should therefore be used with caution in patients with severe hepatic disease.

8. Acidosis and reduced plasma protein concentration, frequently seen in patients with chronic renal dysfunction, may increase the risk of systemic toxicity (SEE DOSAGE AND ADMINISTRATION). Normally there is no need to modify the dose of ropivacaine in patients with impaired renal function when used for single dose or short term treatment. However these patients may be more sensitive to the effects of fentanyl and the possibility of fentanyl accumulation should be kept in mind. Dosage reduction may be necessary in patients with impaired renal function, particularly towards the end of the infusion.

9. The possibility of hypotension and bradycardia following epidural and intrathecal blockade should be anticipated and precautions taken, including the prior establishment of an intravenous line and the availability of vasopressor drugs, vagolytic drugs and oxygen.

10. Local anaesthetics should be given with caution (if at all) to patients with pre-existing neurological disease.

11. Ropivacaine should be used with caution in patients with known drug sensitivities.

12. Naropin with fentanyl should be used with caution in patients with severe impairment of respiratory function. In such patients opioid agonists, such as fentanyl, may further decrease respiratory drive. Patients should be monitored for signs of respiratory depression and appropriate countermeasures taken as necessary.
13. Fentanyl may cause spasm of the Sphincter of Oddi.

14. Fentanyl has abuse potential. Psychological and physical dependence may occur with repeated or prolonged dosing.

15. Hyperglycaemia has been reported with opioid agonists. This should be considered when diabetics require treatment with these agents.

16. Naropin with fentanyl may cause drowsiness and lower limb weakness. Patients should be supervised with initial ambulation to provide assistance where required.

17. Careful and constant monitoring of cardiovascular and respiratory vital signs and the patient’s state of consciousness should be accomplished after each local anaesthetic 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.

18. Local anaesthetics should be given with great caution (if at all) to patients with pre-existing abnormal neurological pathology, e.g. myasthenia gravis. Use with extreme caution in epidural, caudal and spinal anaesthesia when there are 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.

19. Patients treated with class III anti-arrhythmic drugs (e.g. amiodarone) should be under close surveillance. ECG monitoring should also be considered, since cardiac effects may be additive.

20. There have been 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.

21. NAROPIN 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.

Genotoxicity

Ropivacaine hydrochloride was negative in the Ames salmonella/mammalian microsome mutagenicity test, human lymphocyte chromosome aberration test, mouse micronucleus test, E. coli differential DNA repair test, E. coli host-mediated DNA repair test in mice, and the somatic mutation and recombination test in Drosophila melanogaster (fruit fly), and weakly mutagenic in the mouse lymphoma test. The clinical use of ropivacaine is unlikely to pose any risk of genotoxicity.

Fentanyl showed no evidence of genotoxic potential in standard assays for gene mutations, chromosomal damage and other genotoxic effects.
Animal studies have not been done to assess the potential for mutagenic activity when ropivacaine is given in combination with fentanyl.

**Carcinogenicity**

Long term animal assays of carcinogenic potential have not been performed with ropivacaine hydrochloride.

The carcinogenic potential of fentanyl has not been investigated.

Animal studies have not been done to assess the potential for carcinogenic activity when ropivacaine is given in combination with fentanyl.

**Effects on fertility**

No adverse effects on fertility and reproductive performance were seen in rats over 2 generations following daily subcutaneous administration of ropivacaine from prior to mating through weaning, with estimated systemic exposure (plasma AUC) twice the clinical exposure following a 200 mg epidural dose. Increased pup loss in the first 3 days post partum was attributed to reduced maternal care.

Animal studies have not been done to assess the potential for impairment of fertility when ropivacaine is given in combination with fentanyl.

**Use in pregnancy  Category C**

**Ropivacaine - Category B1**

There was no evidence of teratogenicity following daily subcutaneous administration of ropivacaine to rats and rabbits during the period of organogenesis, with estimated systemic exposure (plasma AUC) twice the clinical exposure following a 200 mg epidural dose. In rats treated similarly with ropivacaine daily from late gestation to weaning, there were no treatment-related effects on late foetal development, parturition, lactation, neonatal viability, or offspring growth. In rats treated from late gestation to weaning, maternal toxicity was elicited at a lower dose and lower unbound plasma concentration with bupivacaine than with ropivacaine.

There are no clinical studies in pre-term pregnant women on the effects of ropivacaine on the developing fetus. Ropivacaine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The use of ropivacaine in obstetrics is well documented and no negative effects have been observed.

**Fentanyl - Category C**

Fentanyl crosses the placenta in humans and has been found in fetal blood at concentrations approximately 40% of those found in maternal blood. The safe use of fentanyl in pregnant women has not been established with respect to possible adverse effects on the fetus or on fetal development. Opioid analgesics used during labour may cause respiratory depression in the newborn infant and should be used only after weighing the needs of the mother against the risk to the fetus. Withdrawal
symptoms in newborn infants have been reported with prolonged use of this class of drugs.

**Ropivacaine and fentanyl**
Animals studies have not been done to assess the potential for adverse effects on pregnancy or on the fetus when ropivacaine and fentanyl are given in combination.

**Use during lactation**
Subcutaneous administration of ropivacaine to rats from late gestation to weaning, with estimated systemic exposure (plasma AUC) twice the clinical exposure following a 200 mg epidural dose, did not effect late foetal development, parturition, lactation, neonatal viability, or offspring growth. Ropivacaine and/or its metabolites are excreted into milk in rats, but excretion into human milk has not been investigated.

Small amounts of fentanyl have been detected in breast milk.

**Interactions**

*Local anaesthetics and Antiarrhythmic Drugs*
Naropin with fentanyl should be used with caution in patients receiving other local anaesthetics, agents structurally related to amide type local anaesthetics or other opioids since the toxic effects may be additive.

**Adrenaline**
The duration and intensity of ropivacaine sensory block is not improved by the addition of adrenaline.

**CNS Depressants**
The depressant effects of fentanyl are potentiated by other CNS depressant drugs such as alcohol, tranquilizers, benzodiazepines, barbiturates, neuroleptics, opioids and general anaesthetics.

**Alkaline solutions**
The solubility of ropivacaine is limited at pH values above 6.0. This must be taken into consideration if adding an alkaline solution since precipitation might occur at higher pH values.

**Cytochrome P450 Interactions**

*Fluvoxamine*
There is a potential risk for metabolic interaction when Naropin is used in combination with a potent cytochrome P450 (CYP 1A2) inhibitor, e.g. fluvoxamine. Oral fluvoxamine treatment caused a 70% decrease in ropivacaine clearance and a 3-fold higher AUC in healthy volunteers. Single administrations of ropivacaine should be used with care in patients who are concomitantly receiving a potent CYP 1A2 inhibitor. Repeated administration or long term infusion should be avoided in such patients.

*Ketoconazole*
Co-administration with ketoconazole, a potent inhibitor of CYP3A4, has been shown to cause a marginal (15%) decrease in ropivacaine clearance in healthy volunteers.
**Theoretical Interactions**

Cimetidine, an inhibitor of CYP2E1, did not inhibit the formation of 3-hydroxyropivacaine but inhibited some formation of minor metabolites *in vitro*. A theoretical possibility of metabolic drug interactions with potent inhibitors of CYP1A2, such as enoxacin, may exist.

A theoretical possibility of metabolic ropivacaine drug interactions with other substances known to be metabolised by CYP1A2 such as theophylline, imipramine (also by CYP2D6, CYP2C19) and oestrogens may exist, as with potent inhibitors such as verapamil.

**Neuroleptics**

When a neuroleptic such as droperidol is used with fentanyl, pulmonary arterial pressure may be decreased. Hypotension can occur and, possibly, hypovolaemia (which should be managed with appropriate parenteral fluids). The following adverse reactions have also been reported: chills, shivering, restlessness, hypertension, postoperative hallucinatory episodes and transient periods of mental depression. Extrapyramidal symptoms (dystonia, akathisia and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with antiparkinson agents.

**MAO inhibitors**

Severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. Since the safety of Naropin with fentanyl in this regard has not been established, the use of fentanyl in patients who have received monoamine oxidase inhibitors within 14 days is not recommended (see CONTRAINDICATIONS).

**Nitrous oxide**

Nitrous oxide has been reported to produce cardiovascular depression when given with high doses of fentanyl.

**Amiodarone**

Profound bradycardia, sinus arrest and hypotension have occurred when patients receiving amiodarone have been given fentanyl.

**Beta-Adrenergic Blockers and Calcium Channel Blockers**

The combination of calcium channel blockers and beta-adrenergic blockers during fentanyl anaesthesia should be used with caution since severe hypotension has been reported to occur.

Coadministration of the following drugs may enhance or prolong the effects of fentanyl: azole antifungals, macrolide antibiotics and protease inhibitors such as Ritonavir.

Coadministration of the following drugs may decrease the plasma concentration of fentanyl: phenytoin.

Coadministration of sibutramine hydrochloride with fentanyl may increase the risk of serotonin syndrome (hypertension, hypothermia, myoclonus and mental status changes).
The concurrent administration of fentanyl and naltrexone precipitates opioid withdrawal symptoms.

**Metabolic Interactions**

With the low to intermediate hepatic extraction ratio of ropivacaine (mean 0.4), a fall in the liver blood flow is not expected to have a significant influence on ropivacaine clearance (see PRECAUTIONS).

There was no metabolic interactions between ropivacaine and fentanyl when given in a fixed combination as a continuous epidural infusion for one month in dogs.

**Clinical relevance of interactions**

Patients in clinical studies usually received Naropin with fentanyl in combination with several other therapies. The safety evaluation of Naropin with fentanyl is therefore based upon its use in combination with various concomitant treatments. The review of safety data in these studies show that Naropin with fentanyl has a safety profile comparable to other local anaesthetics used for epidural anaesthesia. Furthermore, drugs metabolised by CYP1A2, e.g. paracetamol, have also been used in combination with Naropin with fentanyl in the clinical programme, without clinical evidence of metabolic interactions.

**ADVERSE EFFECTS**

Adverse reactions to ropivacaine are rare in the absence of overdosage or inadvertent intravascular injection. Adverse reactions to fentanyl are similar to those observed with other opioid agonist analgesics. The adverse reactions to Naropin with fentanyl are similar to those observed with the individual agents.

These adverse reactions are, in general, dose related and may result from high plasma levels caused by excessive dosage, rapid absorption or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. They should be distinguished from the physiological effects of the nerve block itself e.g. a decrease in blood pressure and bradycardia during epidural anaesthesia.

Pronounced acidosis, hyperkalaemia or hypoxia in the patient may increase the risk and severity of toxic reactions.

The effects of systemic overdose and unintentional intravascular injection may involve the central nervous system and/or the cardiovascular system (see OVERDOSAGE). Inadvertent subarachnoid injection may lead to CNS depression, respiratory arrest and cardiovascular collapse.

The following list of adverse events is based upon experience with the monotherapies in their usual dosage range. These events are considered to be of clinical importance, regardless of causal relationship.

**Very common events (>10%)**

**Cardiovascular:** Hypotension
Gastrointestinal: Nausea

Common Events (>1%)

Cardiovascular: Bradycardia, hypertension and tachycardia.

Nervous system: Paraesthesia, temperature elevation, rigors (chills), headache and dizziness.

Gastrointestinal: Vomiting.

Other: Urinary retention, back pain, insomnia, chest pain and oliguria.

Uncommon Events (<1%)

Acute systemic toxicity: More serious but less common reactions that reflect acute systemic toxicity, include dysarthria, muscular rigidity, muscle twitching, myclonic movements, muscle rigidity with laryngospasm or bronchospasm, unconsciousness, convulsions, hypoxia, hypercapnia, apnoea, respiratory depression, severe hypotension and bradycardia, arrhythmias, cardiac arrest. Indirect cardiovascular effects (hypotension, bradycardia) may occur after epidural administration, depending on the extent of the concomitant sympathetic block.

Psychiatric: Anxiety

Nervous System: Hypoesthesia

Vascular: Syncope

Respiratory, thoracic and mediastinal: Dyspnoea

General disorders and administration site conditions: Hypothermia

Rare (≤0.1%)

Cardiac disorders: Cardiac arrest, cardiac arrhythmias

General disorders and administration site conditions: Allergic reactions (anaphylactoid reactions, angioneurotic oedema and urticaria)

These reactions are more frequent after spinal anaesthesia

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

Class related adverse drug reactions

This section includes complications related to anaesthetic technique regardless of the local anaesthetic used.
Neurological complications
Neuropathy and spinal cord dysfunctions (e.g., anterior spinal artery syndrome, arachnoiditis, cauda equina syndrome), have been associated with intrathecal and epidural anaesthesia.

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

Allergic reactions: Allergic reactions (in the most severe instances anaphylactic shock) to local anaesthetics of the amide type or to fentanyl are rare.

Neurological: Neuropathy and spinal cord dysfunction (e.g., anterior spinal artery syndrome, arachnoiditis, cauda equina syndrome) have been associated with regional anaesthesia, regardless of the local anaesthetic drug used. Convulsions have been observed following unintended intravascular injection of ropivacaine.

Other:
Blurred vision, miosis, diaphoresis, postoperative mental depression, paradoxical CNS excitation, delerium and spasm of the sphincter of Oddi.

Clinical Trials using Naropin 2 mg/mL with fentanyl 2 µg/mL
Clinical trials in patients undergoing epidural infusion for postoperative pain show that the following events were more common in patients receiving Naropin with fentanyl than in the group receiving Naropin alone: pruritus, ileus, hypomagnesia, hypoglycaemia, atelectasis, urine abnormal, laboratory test abnormal.

The following events were less common in the Naropin with fentanyl group than in the plain Naropin group: hypothermia, chest pain, vasospasm, coughing.

DOSAGE AND ADMINISTRATION
Naropin with fentanyl should not be mixed with other solutions as no compatibility studies have been conducted. The solubility of ropivacaine is limited at pH > 6.0 and precipitation may occur if mixed with alkaline solutions.

Naropin with fentanyl should only be used by or under the supervision of clinicians experienced in epidural anaesthesia.

Naropin with fentanyl Polybags do not contain a preservative and are intended for single use only. Any solution remaining after 24 hours should be discarded.

Tolerability varies between patients. The lowest dosage that results in effective analgesia should be used and should be based on the status of the patient and the analgesia required. Careful observation of the patient must be maintained during the infusion.

The following table is a guide to dosage. The clinician’s experience and knowledge of the patient’s physical status are of importance when deciding the dose. No data
are available for infusion rates greater than 14 mL/hour or infusion times longer than 72 hours.

**Adults**
Recommended dosages for Naropin with fentanyl in the average, healthy 70 kg adult patient for up to 72 hours.

<table>
<thead>
<tr>
<th><strong>Epidural administration Continuous Infusion</strong></th>
<th><strong>Volume mL/hour</strong></th>
<th><strong>Dosage</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume mL/hour</td>
<td>ropivacaine mg/hour</td>
<td>fentanyl µg/hour</td>
</tr>
<tr>
<td>Naropin 2mg/mL + fentanyl 2µg/mL</td>
<td>6-14</td>
<td>12-28</td>
</tr>
<tr>
<td>Naropin 2mg/mL + fentanyl 4µg/mL</td>
<td>6-14</td>
<td>12-28</td>
</tr>
</tbody>
</table>

**NOTE:**
Careful aspiration before and during injection is recommended to avoid intravascular injection.

1. **Test Dose**

For epidural analgesia, a 3-5 mL test dose of a local anaesthetic solution, preferably containing 5 µg/mL of adrenaline (e.g Xylocaine 2% with adrenaline 1:200,000) should be administered. Verbal contact and repeated monitoring of heart rate and blood pressure should be maintained for 5 minutes following the test dose after which, in the absence of signs of intravascular or intrathecal injection, the main dose may be administered.

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 or signs occur, the infusion should be stopped immediately.

2. **Analgesia**

When calculating the dosage for postoperative analgesia, the use of intraoperative local anaesthetics and opioids should be taken into account.

When prolonged blocks are used, either by continuous infusion or repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. Cumulative doses of up to 800 mg ropivacaine for surgery and postoperative analgesia administered over 24 hours were well tolerated, as were postoperative continuous epidural infusions of ropivacaine with 2 µg or 4 µg fentanyl at rates up to 14 mL/hour for 72 hours.

**Use in Children**

Until further experience has been gained, Naropin with fentanyl is not recommended for use in children below the age of 12 years.
Use in Debilitated or Elderly Patients

Debilitated or elderly patients, including those with partial or complete heart conduction block, advanced liver disease or severe renal dysfunction should be given reduced dosage commensurate with their physical condition. Clinical studies with this group of patients have not been performed (see PRECAUTIONS).

OVERDOSAGE

Acute emergencies associated with the use of local anaesthetics are generally related to high plasma levels or to unintended subarachnoid injection of the solution (see ADVERSE REACTIONS and PRECAUTIONS).

Accidental intravascular injections of local anaesthetics may cause immediate toxic effects. Toxic effects may also arise from exceptionally rapid absorption from highly vascularised areas. 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. Systemic toxic reactions may involve the central nervous system and the cardiovascular system. CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively.

Symptoms

There have been no reports of overdosage in patients receiving Naropin with fentanyl. The symptoms of Naropin with fentanyl overdosage are expected to reflect those seen with overdosage of the individual drugs. Systemic toxic reactions of ropivacaine may involve the central nervous system and the cardiovascular system.

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.

Unconsciousness and grand mal convulsions may follow, which can last from a few seconds to several minutes. Hypoxia and hypercapnia occur rapidly during convulsions due to the increased muscular activity, together with disruption to respiration and possible loss of functional airways. In severe cases apnoea may occur. Respiratory and metabolic acidosis, hyperkalaemia, hypocalcaemia and hypoxia increase and extend 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 should be rapid unless large amounts of the drug have been injected.

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 NAROPIN 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. However in rare cases, cardiac arrest has occurred without prodromal CNS effects.

Large doses of fentanyl can cause respiratory depression.

**Treatment**

If signs of acute toxicity appear, injection of the infusion solution should be immediately stopped.

Treatment consists of ensuring adequate ventilation and arresting convulsions. In the presence of hypoventilation or apnoea, oxygen should be administered and respiration assisted or controlled as necessary. A patent airway must be maintained.

Respiratory depression due to fentanyl can be managed by assisted or controlled respiration or where appropriate by the administration of an opioid antagonist such as naloxone. The duration of respiratory depression of doses of fentanyl employed during anaesthesia is usually longer than the duration of opioid antagonist action. Consult the individual Product Information before administering opioid antagonists.

If convulsions occur and do not spontaneously stop within 15-20 seconds, an anticonvulsant should be given intravenously e.g. diazepam 5-10 mg i.v. or where indicated, sodium thiopentone (5 mg/kg). If convulsions interfere with breathing and/or are not rapidly controlled by specific anticonvulsant medication, suxamethonium (1-2 mg/kg) may be used to paralyse the patient. Artificial ventilation must then be instituted.

If cardiovascular depression is evident (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor and or inotropic agents should be considered.

If ventricular fibrillation, cardiac arrest or circulatory arrest occur, cardiopulmonary resuscitation must be instituted and maintained for a prolonged period if necessary. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

Should cardiac arrest occur, prolonged resuscitative efforts may be required to improve the possibility of a successful outcome.

**PRESENTATION AND STORAGE CONDITIONS**

**Naropin 0.2% with fentanyl 200µg/100mL**

**Naropin 0.2% with fentanyl 400µg/200mL**
(Naropin 2 mg/mL with fentanyl 2 µg/mL)

100 mL, 200 mL Polybag® infusion bags
Naropin 0.2% with fentanyl 400µg/100mL
Naropin 0.2% with fentanyl 800µg/200mL
(Naropin 2 mg/mL with fentanyl 4 µg/mL)
100 mL, 200 mL Polybag® infusion bags

Naropin with fentanyl Polybag® presentations are in a sterile AstraZeneca Theatre Pack®

Naropin with fentanyl Polybag® presentations have a shelf-life of 24 months when stored below 30°C.

Do not freeze.

Polybag® must not be re-autoclaved.

NAME AND ADDRESS OF MANUFACTURER / DISTRIBUTOR

AstraZeneca Pty Ltd
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POISON SCHEDULE OF MEDICINE

S8 – Controlled drug

Date of Approval: 13th April 2011

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