



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report
for
Ropivacaine

Proprietary Product Name: Naropin
Submission No: PM-2009-01406-3-1
Sponsor: AstraZeneca Pty Ltd



April 2010

Contents

I.	Introduction to Product Submission	3
	Product Details	3
	Product Background.....	3
	Regulatory Status	4
	Product Information	4
II.	Quality Findings	4
	Drug Product	4
	Quality Summary and Conclusions.....	4
III.	Nonclinical Findings	4
	Introduction.....	4
	Toxicology	5
	Toxicokinetics	5
	Nonclinical Summary and Conclusions	6
IV.	Clinical Findings	6
	Introduction.....	6
	Pharmacodynamics	7
	Pharmacokinetics	7
	Efficacy	8
	Safety	13
	Clinical Summary and Conclusions	14
V.	Pharmacovigilance Findings	15
VI.	Overall Conclusion and Risk/Benefit Assessment	15
	Quality.....	15
	Nonclinical.....	15
	Clinical.....	16
	Risk-Benefit Analysis	17
	Outcome.....	20
	Attachment 1. Product Information	20

I. Introduction to Product Submission

Product Details

<i>Type of Submission</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	2 March 2010
<i>Active ingredient(s):</i>	Ropivacaine
<i>Product Name(s):</i>	Naropin
<i>Sponsor's Name and Address:</i>	AstraZeneca Pty Ltd Alma Road North Ryde NSW 2113
<i>Dose form(s):</i>	Solution
<i>Strength(s):</i>	0.2% (2 mg/mL)
<i>Container(s):</i>	Polyamp DuoFit ampoules. Polybag infusion bags.
<i>Pack size(s):</i>	Polyamp DuoFit ampoules: 10 mL, 20 mL Polybag infusion bags: 100 mL, 200 mL
<i>Approved Therapeutic use:</i>	Continuous wound infusion for post operative pain management (adults only)
<i>Route(s) of administration:</i>	Continuous wound infusion
<i>Dosage:</i>	2 mg/mL (0.2%) at 4-10mL/h for up to 48 hours

Product Background

AstraZeneca Pty Ltd has applied to extend the indications for Naropin 0.2% (2 mg/mL) to include analgesia by continuous or intermittent postoperative wound infusion at 4-10 mL/h for up to 48 hours in adults and children over 12 years of age. Naropin is currently approved in Australia for:

Surgical anaesthesia (Adults and children over 12 years of age)

- epidural block for surgery including caesarean section
- intrathecal anaesthesia
- field block (minor nerve block and infiltration)
- major nerve block

Analgesia (Adults and children over 12 years of age)

- continuous epidural infusion or intermittent bolus epidural administration for analgesia in postoperative pain or labour pain
- field block (minor nerve block and infiltration)
- continuous peripheral nerve block infusion or intermittent injections for post operative pain management.

Analgesia (Children aged 0-12 years)

- Caudal epidural block in neonates (> 37 weeks gestation and over 2500 g weight), infants and children up to and including 12 years.
- continuous epidural infusion in infants (> 30 days and over 2500 g weight) and children up to and including 12 years
- Peripheral nerve block in children aged 1 up to and including 12 years

For peri- and postoperative pain management.

There are no safety or efficacy data to support the use of Naropin for analgesia for longer than 72 hours. Data for peripheral nerve block administered as a continuous peripheral infusion or intermittent injections support the use for up to 48 hours only.

The indication sought is for: analgesia (adults and children >12 years of age); by: - continuous or intermittent wound infusion. The proposed dosage for this new analgesia technique is 0.2% (2mg/mL) 4-10 mL/h (8-20mg/h for up to 48 hours. The route of administration is by wound infusion via a surgical wound catheter.

A multitude of techniques, often using drugs off label, have been proposed for post operative analgesia reflecting the improved duration and safety of available drugs and devices, particularly in the last 30 years. Of note is the technique of intravenous infusion of local anaesthetics, (mainly procaine, chlorprocaine and lignocaine) for analgesia in subacute and chronic pain¹.

The sponsor submits that the current indications for Naropin do not cover the technique of continuous or intermittent post-operative surgical wound infusion. This technique was made popular by the marketing of lightweight portable infusion devices that it is proposed enable earlier mobilisation and discharge for some procedures.

When comparing the systemic exposure of long acting local anaesthetics, ropivacaine appears to have slightly less cardiac and central nervous system toxicity than levobupivacaine, which in turn is less toxic than bupivacaine. Ropivacaine is also less potent than levobupivacaine or bupivacaine, an effect seen clinically only when low doses are administered.

Regulatory Status

Ropivacaine is a local anaesthetic which was initially registered in Australia in 1995 with expanded indications and dosage modifications in 2000. The current application is unique to Australia.

Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Product

There are two products involved in this application:

- Naropin 0.2% ropivacaine HCl 200mg/100mL injection bag
- Naropin 0.2% ropivacaine HCl 400mg/200mL injection bag

Quality Summary and Conclusions

There was no requirement for a quality evaluation in an application of this type.

III. Nonclinical Findings

Introduction

No nonclinical studies with ropivacaine by the proposed new administration route - continuous or intermittent wound infusion - were provided in the submission. In support of the application, the sponsor submitted one dog study using continuous intra-articular infusion and literature references, and referred to previously evaluated studies in rats by intrathecal administration and in dogs by epidural infusion. The intra-articular study in dogs and a published study in pigs by continuous infusion for femoral nerve block are evaluated below.

¹ Cousins & Bridenbaugh Neural Blockade in clinical anaesthesia and management of pain 2nd ed., p.920.

Toxicology

Dogs

Beagle dogs (12-14 months of age, 10-16 kg) were administered ropivacaine (2 or 5 mg/mL) into the knee joint by infusion over 6 hours. The animals were reused from a previous study and anaesthetised during the infusion. The study was performed in two phases. In phase 1 (technical feasibility study), 2 dogs (1/sex) received 2 mg/mL ropivacaine into one knee joint and 5 mg/mL into the other knee joint, for 6 hours. In phase 2 (dose-finding study), 4 groups of dogs (1/sex/group) were administered 2 or 5 mg/mL ropivacaine by a single 6 hour infusion or three 6 hour infusions over a period of 5 days. Saline as the control was administered into the other knee joint in the phase 2 study. The infusion rate was 0.32 mL/kg/h in both phases. The total ropivacaine dose each dog received was 13.44 mg/kg in the phase 1 study, and 3.84 or 9.6 mg/kg, for each 6 hour infusion, in the phase 2 study. The dogs were killed on day 5 (phase 1) or day 4 after the last dose (phase 2). Blood samples were collected from phase 2 animals before infusion, 3 and 6 hours after infusion start and 10 and 30 minutes, 1, 2 and 4 hours after the end of infusion (last dose of the repeated doses). Plasma ropivacaine concentrations were measured using liquid chromatography (LC) and electrospray tandem mass spectrometry (MS). Vehicle formulation was not reported, but it was presumably saline.

There were no noteworthy clinical signs after infusion. No gross lesions were observed at necropsy (only local tissues were examined for pathological changes). Histological examination of the joints showed minimal inflammation (mixed mononuclear cells and neutrophilic granulocytes) in the synovium of some joints infused with saline and in one joint infused with 2 mg/mL ropivacaine. Slightly more pronounced inflammation (graded as slight) was observed in 3 animals infused with 5 mg/mL ropivacaine.

Pigs

Myotoxic effects of ropivacaine and bupivacaine were compared in pigs.² Femoral nerve block catheters were inserted in anesthetized female pigs (3 months old), and either 20 mL of bupivacaine (5 mg/mL; left leg) or ropivacaine (7.5 mg/mL; right leg) was injected (n=8). Subsequently, bupivacaine (2.5 mg/mL) and ropivacaine (3.75 mg/mL) were continuously infused (8 mL/h) over 6 h. Control animals were treated with normal saline (n=2; left and right legs). After 7 and 28 days (n=4/time point), muscle samples were dissected at the injection sites, and muscle damage was histologically assessed blindly (score: 0 = no damage to 3 = marked lesions/myonecrosis). No morphological tissue changes were detected in the control animals. The two local anaesthetics induced morphologically identical lesions of calcific myonecrosis, formation of scar tissue, and fibre regeneration, but the findings for bupivacaine were more pronounced than those of ropivacaine. Toxicokinetic data were not obtained in this study.

Toxicokinetics

Dogs

Ropivacaine was detectable in all animals, with maximal plasma concentration (C_{max}) 3.3-7.6 $\mu\text{mol/L}$ in the low dose (LD) groups (2 mg/mL) independent of the number of doses and 7.6-8.9 $\mu\text{mol/L}$ after a single infusion and 12-16 $\mu\text{mol/L}$ after 3 infusions in the high dose (HD) groups (5 mg/mL). The time to maximal plasma concentration (t_{max}) was within 1 hour of the end of infusion (6-7 hours after the start of infusion). The area under the plasma concentration time curve from zero to time t (AUC_{0-t}) ranged from 17 to 55 $\mu\text{mol.h/L}$ in the low dose groups and was 66 $\mu\text{mol.h/L}$ (single infusion) and 68-110 $\mu\text{mol.h/mL}$ (repeat infusions) in the high dose groups. Plasma

² Zink W *et al.* The long term myotoxic effects of bupivacaine and ropivacaine after continuous peripheral nerve blocks. *Anesth Analg* 2005; 101: 548-554.

ropivacaine was detectable at the last sampling point (10 hours after the end of infusion) in all animals (0.3-2.5 µmol/L at the LD, 1.9-5.7 µmol/L at the HD).

As this study examined the local effects of intra-articular administration rather than the route anticipated for clinical usage (postoperative wound), the findings are not directly relevant to the current submission.

Nonclinical Summary and Conclusions

The application was for an extension of indications for Naropin 0.2% (2 mg/mL) for analgesia by continuous or intermittent postoperative wound infusion. Naropin 0.2% has been approved for analgesia by continuous or intermittent peripheral nerve block infusion. The proposed infusion rate and duration (4-10 mL/h for up to 48 hours) for wound infusion are similar to those for the already approved peripheral nerve block infusion (5-10 mL/h for up to 48 hours). Therefore, the potential systemic exposure of patients to ropivacaine from the proposed wound infusion is not expected to be significantly different from that occurring with peripheral nerve block infusion. The main nonclinical issue is local effects on wound healing and local toxicity at the site of infusion.

No nonclinical studies by the proposed route of administration were provided in the submission. The sponsor acknowledged in its *Nonclinical Overview* that a study to address local tissue toxicity may be required, but indicated that animal studies by related routes of administration (intrathecal, epidural and intra-articular) provided reassurance of a lack of local tissue toxicity after continuous or intermittent wound infusion. However, none of the studies (intrathecal, epidural, intra-articular) have addressed the potential effects on local tissues by infusion into a surgical wound. Relevant to this application is one published (not GLP-compliant) study in pigs, which were treated with ropivacaine (7.5 mg/mL) for 6 hours at 8 mL/h by continuous peripheral nerve block infusion. In the pig study, continuous infusion of ropivacaine induced muscle damage including myonecrosis, inflammatory cell infiltration, calcification, formation of scar tissue and fibre regeneration 7 and/or 28 days after treatment.² Greater toxicity to local tissues was observed for bupivacaine (2.5 mg/mL). Myotoxicity in the pig study was associated with a ropivacaine concentration 3.75 times the concentration of Naropin; the effects of other ropivacaine concentrations (including that proposed for the clinical indication, 2 mg/mL) were not tested. An improved study design may have obtained useful information on a potential concentration-myotoxicity relationship in this animal model by investigating the effects of a range of concentrations, including 2 mg/mL. In addition, this study may have been more predictive if it had examined the effects of infused ropivacaine on a postoperative wound rather than intact muscle. Nevertheless, the reported study findings suggest that wound infusion of ropivacaine may cause muscle damage and delay wound healing in patients.

Based on the available nonclinical data and the absence of any animal studies with ropivacaine administration by wound infusion, the proposed indication of postoperative analgesia by wound infusion should not be approved unless the potential for adverse effects on local tissues has been adequately assessed in the clinical data.

IV. Clinical Findings

Introduction

The clinical submission consisted of the following published information:

- 11 studies of efficacy and safety in which a total of 328 patients received ropivacaine (in 8 studies at 0.2%, in 8 studies at 4-5 mL/h, in 2 studies by boluses), 227 received placebo and 92 received an active comparator. The duration of 9 of the studies was 48 hours (with 2 of them for 55 hours) while the other 2 were for 24 hours;
- 11 studies evaluable for safety only, in which 399 patients received ropivacaine (0.15-0.75% in 9 studies for 48 hours (with 3 of them for 72 hours and 1 for 96 hours), in 4 studies by boluses.
- 4 reviews.

The literature search strategy was reviewed by TGA and was considered satisfactory.

Pharmacodynamics

In one study,³ venous unbound plasma ropivacaine levels (measured 30 minutes after bolus) passed the lower limit of onset of toxicity (0.34-0.85 mg/L) in 50% of patients, but no signs of toxicity occurred. This study was with intermittent boluses post caesarean section, that is, patients with a markedly altered status (for example, acid-base, serum proteins and circulation).

Pharmacokinetics

In assessing the effects of wound infiltration across studies, the site of infusion may contribute to variations in plasma levels,⁴ as well as the rate of infusion with bolus (or rapid brief) infusion likely to give higher C_{max} than constant infusions.⁵

Unbound (to alpha₁-acid glycoprotein [AAG]) ropivacaine is ~ 4% of the total and the active metabolite 2',6'-pipecoloxylidide (PPX) is ~60% unbound, these being the components that are theoretically responsible for systemic activity. After initial loading of the circulation with ropivacaine and PPX there is a considerable arterial/venous difference as they are taken up by the tissues. It is only when this difference disappears (at equilibrium) that venous concentrations reflect site of action concentrations. This occurs about 30 minutes after intravenous infusion and 1 hour after epidural infusion.

Seven clinical studies had pharmacokinetic (PK) data that were reviewed.

Table 1: PKs of Total and Unbound Venous Plasma Ropivacaine During 96 hour Infusion (Continuous infusion) of Incision-site Ropivacaine (0.2%, 5 mL/h), and Plasma Alpha₁-acid Glycoprotein (AAG) Concentrations Before and 48 hours After Surgery.⁹

	Mean ± SD	Range
Total plasma ropivacaine (n = 5)		
C_{max} (mg/L)	4.5 ± 2.6	2.3-8.8
t_{max} (h)	45.6 ± 29.4	0.75-72
AUC (mg/h per litre)	137 ± 114	22-180
CL (clearance)/F (L/h)	7.9 ± 8.0	2.1-21.5
Unbound plasma ropivacaine (n = 3)		
C_u (Unbound plasma concentration) _{max} (mg/L)	0.068 ± 0.013	0.052-0.087
$t_{u,max}$ (h)	17.2 ± 17.8	2-48
CL_u/F (L/h)	568 ± 81	483-669
f_u (%)	4.0 ± 0.01	0.42-8.05
Plasma AAG (g/L) (n = 5)		
Before surgery	0.85 ± 0.35	0.42-1.39
48h after surgery	1.39 ± 0.17*	1.13-1.55

*P < 0.05. C_{max} , highest total ropivacaine concentration; t_{max} time to C_{max} ; AUC, area under the plasma ropivacaine concentration vs. time curve; $C_{u,max}$ highest unbound ropivacaine concentration; $t_{u,max}$ time to $C_{u,max}$; CL/F, apparent total ropivacaine clearance; CL_u/F , apparent unbound ropivacaine clearance; f_u , unbound ropivacaine fraction in plasma.

³ Fredman et al. The analgesic efficacy of patient controlled ropivacaine instillation after caesarean delivery. *Anesth Analg* 2000; 91: 1436-40.

⁴ Cousins & Bridenbaugh Neural Blockade in clinical anaesthesia and management of pain 2nd ed., p.131.

⁵ Cousins & Bridenbaugh Neural Blockade in clinical anaesthesia and management of pain 2nd ed., p.122.

Most of the studies that measured unbound plasma concentration (C_u) did so only after 24 and 48 hours.^{6,7,8} Corso et al 2007 measured C_u more frequently and derived a number of PK parameters, but since the sampling was venous, the earlier results do not assess toxicity levels.⁹ However all results reported in these studies were well below those reported to cause CNS toxicity (0.34mg/L).

Summary

The PK data suggest the safety of the use of continuous wound infusions post surgery in that unbound concentrations are well below previously described toxic levels.

However the PK data does not support the use of intermittent boluses into the wound in obstetric patients, where the levels reached the lower limit of toxicity and at 6.5 hours appeared to be still rising.

In Fredman et al 2000, 1 hour after 8-10mg spinal bupivacaine, given post caesarean section followed by intermittent boluses: at 6.5 hours $C_{u \text{ venous}}$ was for 5/10 patients ~ 400ng/mL (mean for all 10 ~250ng/mL).³ At 6.5 hours $C_{u \text{ venous}}$ did not appear to have reached a plateau.

Efficacy

The submission included the following trials together with a systematic review that did not cover all of them (Liu et al 2006).¹⁰

Table 2: Randomised Controlled Trials versus placebo

Author	Title
Assessing efficacy in Continuous Wound Infusion	
Beaussier et al 2007 ⁶	Continuous preperitoneal infusion of ropivacaine provides effective analgesia and accelerates recovery after colorectal surgery.
Stewart et al 2004 ¹¹	Randomised trial of a pain control infusion pump following inguinal hernia repair.
Ansaloni et al 2007 ¹²	The analgesic efficacy of continuous elastomeric pump ropivacaine wound instillation after appendectomy.
Bianconi et al	Pharmacokinetics and efficacy of ropivacaine continuous wound installation

⁶ Beaussier et al. Continuous preperitoneal infusion of ropivacaine provides effective analgesia and accelerates recovery after colorectal surgery. *Anesthesiology* 2007; 107: 461-8.

⁷ Blumenthal et al. Continuous infusion of ropivacaine for pain relief after iliac crest bone grafting for shoulder surgery. *Anesthesiology* 2005; 102: 3927.

⁸ Gottschalk et al. Continuous wound infiltration with ropivacaine reduces pain and analgesic requirement after shoulder surgery. *Anesth Analg* 2003; 97: 1086-91.

⁹ Corso et al. Safety of 96 hour incision site continuous infusion of ropivacaine for postoperative analgesia after bowel cancer resection. *Ther Drug Monit* 2007; 29: 57-64.

¹⁰ Liu, J. Efficacy of Continuous Wound infusion Catheters Delivering Local Anaesthetic for Postoperative Analgesia: A Quantitative and Qualitative Systematic Review of Randomized Controlled Trials. *Am Coll Surg* 2006; 203: 914-32.

¹¹ Stewart et al. Randomised trial of a pain control infusion pump following inguinal hernia repair. *ANZ J Surg* 2004; 74: 873-876.

¹² Ansaloni et al. The analgesic efficacy of continuous elastomeric pump ropivacaine wound installation after appendectomy. *J Clin Anesth* 2007; 19: 256-263.

¹³ Bianconi et al. Pharmacokinetics and efficacy of ropivacaine continuous wound installation after joint replacement

2003 ¹³	after joint replacement surgery
Bianconi et al 2004 ¹⁴	The pharmacokinetics and efficacy of ropivacaine continuous wound installation after spine fusion surgery.
Blumenthal et al 2005 ⁷	Continuous infusion of ropivacaine for pain relief after iliac crest bone grafting for shoulder surgery.
Dowling et al 2003 ¹⁵	Improved pain control after cardiac surgery: results of a randomised, double-blind, clinical trial.
Forastiere et al 2008 ¹⁶	Effectiveness of continuous wound infusion of 0.5% ropivacaine by On-Q pain relief system for postoperative pain management after open nephrectomy.
Gottschalk et al 2003 ⁸	Continuous wound infiltration with ropivacaine reduces pain and analgesic requirement after shoulder surgery.
Assessing efficacy in Intermittent Wound Infusion	
Fredman et al 2000	The analgesic efficacy of patient-controlled ropivacaine instillation after caesarean delivery.
Rawal et al 2006 ¹⁷	Pain relief following breast augmentation surgery: a comparison between incisional patient controlled regional analgesia and traditional oral analgesia.

Continuous Wound Infusion

Beaussier et al 2007⁶ The authors suggest that lack of benefit seen using the technique in previous studies was due to subcutaneous siting of the catheter. In this study the catheter was sited on the parietal peritoneum, beneath the transversalis fascia. Details of the study:

- Prospective double blind placebo controlled study centred in France and Switzerland.
- ASA I or II patients for elective resection of colorectal tumours, via periumbilical incision with primary anastomosis.¹⁸

surgery. Br J Anaesth 2003; 91: 830-5.

¹⁴ Bianconi et al. The pharmacokinetics and efficacy of ropivacaine continuous wound installation after spine fusion therapy. Anesth Analg 2004; 98: 166-72.

¹⁵ Dowling et al. Improved pain control after cardiac surgery: Results of a randomized, double-blind, clinical trial. J Thorac Cardiovasc Surg 2003; 126: 1271-8.

¹⁶ Forastiere et al. Effectiveness of continuous wound infusion of 0.5% ropivacaine by On-Q pain relief system for postoperative pain management after open nephrectomy. Br J Anaesth 2008; 101: 841-7.

¹⁷ Rawal et al. Pain relief following breast augmentation surgery: a comparison between incisional - patient controlled regional analgesia and traditional oral analgesia. Eur J Anaesthesiol; 2006; 23: 1010-17.

¹⁸ ASA: The American Society of Anesthesiology Classification system is used by anesthesiologists to stratify severity of patients' underlying disease and potential for suffering complications from general anaesthesia. The following levels are used:

ASA I: Normal healthy patient (Pt)

ASA II: Pt with mild systemic disease; no functional limitation—e.g., smoker with well-controlled BP

ASA III: Pt with severe systemic disease; definite functional impairment—e.g., diabetes and angina with relatively stable disease, but requiring therapy

ASA IV: Pt with severe systemic disease that is a constant threat to life—e.g., diabetes and angina plus CHF; Pts have dyspnoea on mild exertion and chest pain

ASA V: Unstable moribund Pt who is not expected to survive 24 hours with or without the operation

ASA VI: Brain-dead Pt whose organs are removed for donation to another

- General anaesthesia.
- After wound closure, 0.2% ropivacaine via catheter, initial 10mL bolus then 10mL/h continuous infusion.
- On awakening, morphine 2mg boluses based on verbal rating scale.
- All patients had morphine patient controlled analgesia. (PCA).
- Endpoints: morphine consumption (primary endpoint), pain relief, and recovery (multiple assessments).
- Sample size based on a 30% difference in morphine consumption needed 21 patients in each group.
- 49 enrolled, 6 patients excluded for various surgical reasons, 1 control patient had catheter removed early (for an adverse event [AE] - hyperthermia), 21 in each group completed.
- Total morphine consumption was 48 ± 23 mg vs. 84 ± 37 mg ($p = 0.0004$).
- Pain at rest was significantly less in first 12 hours and on coughing for first 48 hours.

Comment: This was from ropivacaine catheter initial bolus and 48 hour infusion only.

Stewart et al 2004¹²

- All patients but 1 received a mesh graft.
- 25 versus 25 patients had 80% power at an $\alpha = 0.05$ for a $\geq 25\%$ reduction in pain score (visual analogue).
- Actual per protocol population (PPP), $n = 24$.
- Mann – Whitney U-test: difference not significant at rest; significant differences on sitting and walking.
- 4mL/h of 7.5mg/mL commenced on skin closure, rescue medication if needed only in first 4 hours.

Comment: No initial loading bolus. Do not appear to have considered as among the alternatives pre-emptive inguinal field block - used for analgesia for this procedure for > 30 years.

Ansaloni et al 2007¹³

- In ropivacaine group: initial bolus dose 10 mL 0.2%, after skin closure commenced an infusion of 0.2%.
- Endpoint was pain on VAS or simple verbal scale (SVS).¹⁹
- Sample size based on a reduction from 60 to 30% of patients having a VAS at rest > 3 at 6 and 12 hours.

Comment: The study report did not actually give the results for the VAS to enable assessment on this basis. It was provided for SVS. VAS was provided only as a comparison of means with SDs.

Bianconi et al 2003¹⁴

In the active group, after fascia closure an infiltration with 40 mL of 0.5% ropivacaine (200 mg), then infusion commenced soon after this (when catheter inserted and after skin closure). The control group received no infiltration and only saline infusion. Sample size was based on a mean difference of 20 mm in VAS. From 4-72 hours, VAS differences between the groups at rest and on mobilisation were statistically significantly different, except at rest at 4 hours. There was no significant difference between rest and passive mobilisation for ropivacaine, while there was for control.

¹⁹ **VAS:** Visual analogue scale: score plotted on 100mm .The repeatability of the score (or imprecision) is ± 20 mm, i.e. a change must be greater than 20mm to confirm a change. A clinically significant change in VAS needs to take this into account.

Comment: The difference was not significant at rest at 4 hours when infiltration was working, only for passive movement.

Bianconi et al 2004¹⁵

In the active group, after fascia closure an infiltration with 40 mL of 0.5% ropivacaine (200mg), then infusion commenced soon after this (when catheter inserted and before skin closure). The control group received no infiltration and only saline infusion. From 4-72 hours VAS differences between the groups at rest and on mobilisation were statistically significantly different, the maximum VAS 72.8 ± 9 vs. 38.9 ± 9.4 at rest and 85.6 ± 7.8 vs. 50.0 ± 4.8 . Sample size was based on a mean difference of 20mm in VAS.

Comment: Most patients complained of severe pain at rest in the first 12 hours, for much of which time the infiltration will be working.

Blumenthal et al 2005⁷

- Interscalene block prior to induction (40 mL 0.5% -200 mg), mean operating time 90 minutes.
- At end of surgery bolus of 30 mL 0.5% ropivacaine, then an infusion of 5 mL/h of 0.2%.
- Continuous interscalene infusion from 6 hours (10 mL 0.2% per hour).
- Sample size was based on a 25% reduction in pain scores at rest in the first 24 hours.
- All patients had PCA morphine.

Comment: Actual numerical results not given but graphically appear to have met the expected endpoint. The differences were statistically significant to 32 hours.

Dowling et al 2003¹⁶

- Ropivacaine patients received bilateral intercostal blocks just prior to closure.
- 40 (20/20) patients gave 80% power for 50% difference in total morphine equivalent dose with 2-sided significance at 0.05.
- Eventual PPP n= 16.
- Mean overall VAS significantly less for ropivacaine (1.6 versus 2.6 p = 0.005) as was total narcotic use (47.3 versus 78.7 p = 0.038).
- All patients had morphine PCA.

Comment: The use of intercostal blocks prior to the infusion confuses the issue, as they may provide analgesia for several hours during the initial recovery when most pain and most mobilisation occurs. They did show less need for analgesia from Day 2, but again this may reflect the effects of early mobilisation.

Forastiere et al 2008¹⁷

- Before incision infiltration with 10 mL 1% ropivacaine and query again at the end of surgery.
- Upon awakening started 48 hours infusion of 4 mL/h 0.5% ropivacaine.
- Primary endpoint mean VAS, Sample size based on a difference of 0.5 point on 10 point VAS at 24 hours.
- All patients had PCA morphine IV.
- VAS at 24 hours 1.7 versus 0 (95% confidence intervals [CI] 1.5-1.9, p = < 0.0001).

Comment: The study was able to show a mean difference of 1 day in length of stay (LOS) (2.1 versus 3.2 days).

Gottschalk et al 2003⁸

- After skin closure 30 mL 7.5mg/mL ropivacaine (20 mL in catheter and 10 mL infiltration).
- Ropivacaine groups then received either 2 mg/mL or 3.75 mg/mL at 5 mL/h.
- All patients had PCA piritramide.
- Sample size 13/group gave a power of 0.8 for a reduction in VAS ≥ 15 mm at 48 hours in ropivacaine 3.75 mg/mL group compared to saline group.

Comment: The actual values for differences in VAS at 24 hours not given, states VAS for 3.75 mg/mL were significantly less at rest ($p < 0.005$) for all the study period and with 2 mg/mL for all except 3 hour and 4 hour results.

Intermittent Wound Infusion

Fredman et al 2000³

Intermittent 10 mL 0.2% ropivacaine, not < 1 hour apart (mean total 7 ± 2 infusions or $67 \text{ mg} \pm 22 \text{ mL}$).

- In first 6 hours, 48% of the ropivacaine group received rescue morphine (versus 92% of control); for $2 \pm 3 \text{ mg}$ vs. $10 \pm 5 \text{ mg}$ of morphine, both differences being significant ($p < 0.01$).

Comment: The determination of sample size was not given. One patient was sufficiently drowsy to fail to close the infusion clamp for 30 minutes.

Rawal et al 2006¹⁹

- Day surgery, done with local infiltration prilocaine 0.5% 123 mL.
- Post operative 10 mL bolus wound infusions 0.25% or 0.5%, at least 1 bolus infusion performed before discharge home.
- Comparator no infusion.
- Sample size based on a 25% decrease in VAS.
- Most VAS were made by patient before and 20 minutes after a bolus (the comparator group had 4 set times in the day to take VAS).
- 2 patients required general anaesthetics (Gas).
- Rescue morphine: 7/30 on ropivacaine required 3.3 ± 2.0 (2-10) mg, while 25/30 of the controls required 6.2 ± 3.1 (2-7) mg.
- After discharge amount of dextropropoxyphene used was similar between groups.

Comment: The decrease in VAS was not defined as to whether it meant a decrease before and after ropivacaine bolus or a decrease in VAS between ropivacaine and control groups. Actual results for ropivacaine were not given, but shown graphically and stated that the decrease before and after bolus was significant ($p = 0.05$) with no significant difference between strength of boluses. The lack of an infusion device for control makes this an open study except for the within-individual comparison of concentrations.

Conclusions regarding efficacy

In relation to continuous infusion: Efficacy was shown by Beaussier et al 2007 with continuous infusion after an initial bolus through the catheter.⁶ Stewart et al 2004 failed to show efficacy in the primary variable at rest but did so on mobilisation, but this may reflect the lack of an initial loading dose.¹² Ansaloni et al 2007 could not be interpreted for the primary variable.¹³ The study by Beaussier et al 2007 was well conducted and included PK data.⁶

All other studies were confounded by the use of other blocks or infiltration prior to the use of the catheter infusion.

In relation to intermittent infusion: Efficacy was not clearly demonstrated. Fredman et al 2000 showed some efficacy in the first 6 hours postoperatively though primary endpoints were not indicated. Of concern, possibly toxic levels were achieved by 6 hours and still rising, when the boluses ceased.¹⁸ Rawal et al 2006 showed that intermittent infusion was ineffective as a good analgesic technique in that patients had a seesawing pain level with VAS rising and falling as wound was intermittently infused.¹⁹ Comparison with control (open) could not readily be made except that analgesic use after discharge was similar.

Safety

Patient exposure

The proposed exposure is 2mg/mL (0.2%) at 4-10 mL for up to 48 hours.

Only 2 continuous infusion studies used the maximum proposed exposure of ropivacaine 2 mg/mL (0.2% w/v) at 10 mL/h for 48 hours.

- Beaussier et al 2007 reported that in 21 patients there were no major adverse events (AEs) (1 discontinuation due to AE was with control).⁶ Severe nausea and vomiting requiring treatment: 2 ropivacaine group versus 6 control may reflect differences in morphine requirements. One patient in each group had residual long term pain. No sign or symptom of systemic toxicity. Highest unbound ropivacaine venous concentration after 24 hour infusion was 0.12 mg/L. Assuming there is a small a-v difference after 24 hours this is unlikely to cause toxicity (arterial lower limit for onset with rapid [10mg/min] infusion is 0.34-0.85 mg/L, at which time venous unbound ropivacaine measured 0.01-0.24 mg/L).²⁰
- Kampe et al 2003 reported experience in 2 patients.²¹ No additional analgesia required, no nausea, vomiting or pruritus. No AEs, no signs of toxicity.
- Pelissier et al 2006 employed ropivacaine 2 mg/mL (0.2% w/v) 10-15 mL/h given for 48 hours in 25 patients.²² Total ropivacaine only on 5 patients on 12.5 mL/h (at 24 hours mean was 2.32mg/L (max 2.55mg/L). One discontinuation due to AE associated with a fistula forming in a patient with carcinoma resection. There were no discontinuations for signs of toxicity.
- In Bonvini et al 2004 (a case study) one patient received ropivacaine 4 mg/mL (0.4% w/v) at 8 mL/h for 48 hours after an initial bolus of 30 mL 0.5% ropivacaine.²³ Free ropivacaine at 48 hours was 0.23µmol/L.

In the published literature submitted, 508 patients received ropivacaine by continuous infusion, 135 by intermittent boluses and 31 twice received 100 mL into the wound.

In the 16 publications using continuous infusion, 11 used 0.2%, 10 used 4 or 5 mL/h and 10 went for 48 hours, with only 2 for < 48 hours, the others going longer than 48 hours.

Total exposure to the drug is not useful given that in most publications there were associated boluses, blocks or infiltrations. Few had infusions of the wound only.

Adverse events

Post-operative nausea and vomiting were higher in control groups and appeared to be in association with greater morphine use. Fever was common in some of the studies but was associated with the surgical diagnosis (for example, appendicectomy).

Wound healing In Rawal et al 2006, 30 patients had 2 infusion catheters inserted and 30 controls had none.¹⁹ 'There was no wound infection and wound healing was good in 59/60 patients. One

²⁰ Knudsen et al Central Nervous and Cardiovascular effects of IV infusions of ropivacaine, bupivacaine and placebo in volunteers; BJA; 1997; 78; 507-514.

²¹ Kampe et al. Concept for postoperative analgesia after pedicled TRAM flaps: continuous wound instillation with 0.2% ropivacaine via multilumen catheters. A report of two cases. Brit Assoc Plastic Surgeons 2003; 56: 478-483.

²² Pelissier et al. Pre-peritoneal continuous infusion of local anaesthetics for pain relief after laparotomy. A preliminary report. Annales de Chirurgie 2006; 131: 198-202.

²³ Bonvini et al. Iliac crest donor site analgesia with ropivacaine infusion after autogenous bone graft. Euro J Anaesth 2004; 21: 237-241.

patient in the tablet (control) group had signs of localised infection in a small area ($< 1\text{cm}^2$) two weeks after surgery; there were no signs of infection at the 1 week control.'

Persistent pain Of the few studies that looked at wound pain persisting some showed a difference (especially on movement) while others showed no difference. Less pain especially on movement would be expected if earlier and better mobilisation occurred.

Adverse reactions (drug-related adverse events)

There were no apparent symptoms of toxicity despite some studies using a considerable volume of local anaesthetic and two patients receiving an inadvertent overdose of 60 mL (and a third had 60 mL of bupivacaine). In some studies patients reported paraesthesia and numbness that related to spread of ropivacaine producing regional nerve block.

Withdrawals due to adverse events

There were 3 discontinuations due to AEs:

1. Fever that settled without treatment.
2. Catheter blocked in association with surgical fistula.
3. Respiratory difficulties, chest pain and T-wave changes associated with a low haemoglobin.

Deaths and other serious adverse events

No deaths, one SAE of a pulmonary embolus (Polglase et al 2007) on ropivacaine.²⁴

Laboratory abnormalities

A few studies made general comment on the lack of difference between ropivacaine and control laboratory results.

Post-marketing experience

Patient exposure can only be estimated on the basis of drug exposure not in relation to technique.

However, a search of AstraZeneca's own safety database produced 2 cases:

1. A death with 8 mL/h infusion for a nephrectomy, considered related to drug (no more info).
2. A grand mal convulsion and death. ASA IV - 20 mL boluses of 0.75% for 24 hours, total ropivacaine concentration 10.3mg/mL, death not considered related to ropivacaine.

Conclusions regarding safety

Continuous wound infusion at the recommended rate and duration appears to have been demonstrated to be safe.

However the safety of intermittent bolus wound infusion has not been well demonstrated - only 30 patients received the recommended dose or greater intermittently for 48 hours, the other studies being shorter or of lesser concentration. Furthermore the demonstration of high unbound ropivacaine levels after 6 hours at the recommended rate in Fredman et al 2000 is of concern.³ Also of concern is that 2 of 135 patients (1.5%) had an inadvertent overdose with the technique.

Clinical Summary and Conclusions

The evaluator recommended that the indications and dosage and administration be extended to include:

²⁴ Polglase et al. Continuous wound infusion of local anaesthetic for the control of pain after elective abdominal colorectal surgery. *Dis Colon Rectum* 2007; 50: 2158-2167.

Continuous wound infusion, at the proposed exposure of 2mg/mL (0.2%) at 4-10 mL for up to 48 hours.

In the opinion of the evaluator, there has been sufficient demonstration of efficacy and safety to support this.

Further the evaluator recommended consideration of an initial loading bolus – in the absence of any other pre-infusion local technique.

The evaluator did not recommend extension to include intermittent wound infusion. Efficacy was not clearly demonstrated, patient exposure was low (the use of 2 x 24 hour boluses of 100mL was not the same technique) and there were several safety concerns.

V. Pharmacovigilance Findings

A Risk Management plan was submitted by the sponsor. No amendments were requested.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in an application of this type.

Nonclinical

The proposed infusion rate and duration (4-10 mL/h for up to 48 hours) for wound infusion are similar to those for the already approved peripheral nerve block infusion (5-10 mL/h for up to 48 hours). Therefore, the potential systemic exposure of patients to ropivacaine from the proposed wound infusion is not expected to be significantly different from that occurring with peripheral nerve block infusion. The main nonclinical issue is local effects on wound healing and local toxicity at the site of infusion.

No nonclinical studies by the proposed route of administration were provided in the submission. The sponsor acknowledged in its Nonclinical Overview that a study to address local tissue toxicity may be required, but indicated that animal studies by related routes of administration (intrathecal, epidural and intra-articular) provided reassurance of a lack of local tissue toxicity after continuous or intermittent wound infusion. However, none of the studies (intrathecal, epidural, intra-articular) have addressed the potential effects on local tissues by infusion into a surgical wound. Relevant to this application is one published (not GLP-compliant) study in pigs, which were treated with ropivacaine (7.5 mg/mL) for 6 hours at 8 mL/h by continuous peripheral nerve block infusion. In the pig study, continuous infusion of ropivacaine induced muscle damage including myonecrosis, inflammatory cell infiltration, and calcification, formation of scar tissue and fibre regeneration 7 and/or 28 days after treatment.² Greater toxicity to local tissues was observed for bupivacaine (2.5 mg/mL). Myotoxicity in the pig study was associated with a ropivacaine concentration 3.75 times the concentration of Naropin; the effects of other ropivacaine concentrations (including that proposed for the clinical indication, 2 mg/mL) were not tested. An improved study design may have obtained useful information on a potential concentration-myotoxicity relationship in this animal model by investigating the effects of a range of concentrations, including 2 mg/mL. In addition, this study may have been more predictive if it had examined the effects of infused ropivacaine on a postoperative wound rather than intact muscle. Nevertheless, the reported study findings suggest that wound infusion of ropivacaine may cause muscle damage and delay wound healing in patients.

Based on the available nonclinical data and the absence of any animal studies with ropivacaine administration by wound infusion, the proposed indication of postoperative analgesia by wound infusion should not be approved unless the potential for adverse effects on local tissues has been adequately assessed in the clinical data.

Clinical

Pharmacokinetics

The clinical evaluator summarised that the pharmacokinetics data support the safety of the use of continuous wound infusions post surgery in that unbound concentrations are well below previously described toxic levels.

However, the PK data do not support the use of intermittent boluses into the wound in obstetric patients, where the levels reached the lower limit of toxicity and at 6.5 hours appeared to still be rising.

Efficacy

The clinical evaluator identified nine randomised placebo controlled published studies assessing the efficacy of ropivacaine in **continuous wound infusion** consisting of:

- Beaussier et al 2007⁶
- Stewart et al 2004¹² - The clinical evaluator commented that there was no initial loading bolus.
- Ansaloni et al 2007¹³ - The clinical evaluator commented that the study report did not actually give the results for the VAS to enable assessment on this basis.

According to the clinical evaluator, all other published articles assessing the efficacy of ropivacaine in continuous wound infusion (Bianconi et al 2003,¹⁴ Bianconi et al 2004,¹⁵ Blumenthal et al 2005,⁷ Dowling et al 2003,¹⁶ Forastiere et al 2008,¹⁷ Gottschalk et al 2003⁸) were confounded by the use of other blocks or infiltration prior to the use of the catheter infusion.

Furthermore, the Delegate noted that those published articles did not use the proposed ropivacaine concentration (0.2%) for which the extension of indications was sought, thereby making them strictly unevaluable for the current submission.

The clinical evaluator identified two publications assessing the efficacy of ropivacaine in **intermittent wound infusion** consisting of:

Fredman et al 2000³ –The clinical evaluator commented that the determination of sample size was not given.

Rawal et al 2006¹⁹ – The Delegate noted that this publication used 0.25% or 0.5% ropivacaine and is therefore rejected in the context of the current submission.

Summarising, the clinical evaluator stated that:

In relation to the continuous infusion, efficacy was shown by Beaussier et al 2007 after an initial bolus through the catheter.⁶ Stewart et al 2004 failed to show efficacy in the primary variable at rest but did not so on mobilisation, this may reflect the lack of an initial loading dose.¹² Ansaloni et al 2007 could not be interpreted for the primary variable.¹³

In relation to the intermittent infusion, efficacy was not clearly demonstrated. Fredman et al 2000 showed some efficacy in the first 6 hours postoperatively though primary endpoints were not indicated.³ Of concern, possibly toxic levels were achieved by 6 hours and still rising, when the boluses ceased. Rawal et al 2006 showed that intermittent infusion was ineffective as a good analgesic technique in that patients had a seesawing pain level with VAS rising and falling as wound was intermittently infused.¹⁹ Comparison with control (open) could not readily be made except that analgesic use after discharge was similar.

Safety

The clinical evaluator stated that the proposed exposure is 2mg/mL (0.2%) at 4-10 mL for up to 48 hours and that only two continuous infusion studies used the maximum proposed exposure of

ropivacaine 2mg/mL (0.2% w/v) at 10mL for 48 hours. The clinical evaluator concluded that continuous wound infusion at the recommended rate and duration appears to be safe. For the intermittent bolus wound infusion, however, the clinical evaluator stated that safety has not been well demonstrated – only 30 patients received the recommended dose or greater intermittently for 48 hours, the other studies being shorter or of lesser concentration. Furthermore, the demonstration of high unbound ropivacaine levels after 6 hours at the recommended rate in Fredman et al 2000 is of concern.³ Also of concern was that 2 of 135 patients (1.5%) had an inadvertent overdose with the technique.

The clinical evaluator stated that a search of Astra Zeneca's own safety database produced 2 cases:

1. A death with 8mL/h infusion for a nephrectomy, considered related to drug (no further information).
2. A grand mal convulsion and death ASA IV 20mL boluses of 0.75% for 24h, total ropivacaine concentration 10.3mg/mL, death not considered related to ropivacaine.

The clinical evaluator recommended that the indications, dosage and administration sections of the product information be extended to include "Continuous wound infusion" at the proposed "2mg/mL (0.2%) at 4-10mL for up to 48 hours" proposed exposure. Furthermore, the clinical evaluator recommended consideration of an initial loading bolus – in the absence of any other pre-infusion local technique.

The clinical evaluator rejected extension to include intermittent wound infusion. Efficacy was not clearly demonstrated, patient exposure was low (the use of 2 x 24 hour boluses of 100 mL is not really the same technique), and there were several safety concerns.

Risk-Benefit Analysis

Following receipt of the clinical evaluation report, the sponsor submitted a response. The sponsor agreed with the evaluator's recommendation to approve the indication of Continuous Wound Infusion (CWI) at the proposed exposure of 2mg/mL (0.2%w/v) at 4-10 mL/h for up to 48 hours. The sponsor did not contend the evaluator's recommendation for Intermittent Wound Infusion and would accept the Delegate's eventual decision in this regard.

The sponsor wished to provide some clarification around a number of statements in the TGA's Clinical Evaluation Report (CER) which it considered potentially misleading.

1. In relation to efficacy studies for CWI (except Beaussier et al 2007,⁶ Ansaloni et al 2007¹³ and Stewart et al 2004¹²) the evaluator commented:

All other studies were confounded by the use of other blocks or infiltration prior to the use of the catheter infusion.

The sponsor agreed that it was true that the studies referred to by the evaluator variously involved administration of ropivacaine as blocks or infiltration into or surrounding wound tissues *prior* to the catheter wound infusion, however, the sponsor did not consider that this confounds or detracts from the overall and consistent findings from the studies. That is, statistically and clinically significant reductions were reported at most or all time points in favour of ropivacaine as compared to saline control for post-operative pain, PCA opioid/analgesic consumption, postoperative nausea and vomiting and other variables where assessed (for example, length of hospital stay, patient satisfaction).^{7,8,14,15,16,17} The persistence of any anaesthetic effect from the pre-infusion administration would vary according to a number of variables (dose, route of administration etc) but normally the effect would last no longer than about 2-6 hours. Given this and that in the implicated studies, assessment periods were either 36 hours (1 study), 48 hours (3 studies) or 72 hours (2 studies), the sponsor did not consider any

masking or confounding effect arising from pre-infusion anaesthetic administration to be significant.^{7,8,14,15,16,17}

Additionally, an expected confounding effect of a pre-infusion block and /or infiltration given to both treatment groups would be to diminish the observed treatment effect of ropivacaine at early time points. Pre-infusion wound infiltration was given to both groups in the Forastiere et al 2008 study and yet at the first time point (at 6 hours) a significant difference in postoperative pain in favour of the ropivacaine group was observed.¹⁷

Pre-infusion blocks and/or infiltration would reflect normal practice and thus the studies give realistic assessment of the technique for the given surgical procedures.

2. The evaluator stated:

Only 2 continuous infusion studies used the maximum proposed exposure of ropivacaine 2mg/mL (0.2%w/v) at 10 mL/h for 48 hours.

The sponsor noted that the maximum proposed exposure equates to a total dose of 20 mg of ropivacaine per hour. Two other studies submitted also achieve this level of exposure, though employing different solution concentrations:

- Stewart et al 2004 uses a continuous infusion of 7.5mg/mL (0.75% w/v) at 4mL /h which equates to 30mg/h, thus exceeding the proposed maximum exposure¹²
- Forastiere et al 2008 uses a continuous infusion of 5mg/mL (0.5% w/v) at 4mL/h which equates to 20mg/h.¹⁷

As the evaluator stated, a number of the submitted studies also involved additional pre-infusion ropivacaine administration, thus adding to the total ropivacaine exposure.

The clinical evaluator commented on the above sponsor's responses as follows:

In relation to the first point, the sponsor has attempted to challenge the possibility of the studies being confounded by previous blocks/infiltration and in particular refers to Forastiere et al.¹⁷ This study showed that the combination of 2 x 10 mL ropivacaine infiltration plus post-operative wound infusion gave a significantly better VAS result than a 2 x 10 mL ropivacaine infiltration alone. The sponsor states that normally the effect of pre-infusion administration would last longer than about 2-6 hours. The study by Horn et al with a combination of infiltration and single drain bolus lasting 10 hours suggests confounding may occur.²⁵

²⁵ Horn et al. Wound infiltration and drain lavage with ropivacaine after major shoulder surgery. *Anesth Analg* 1999; 89: 1461.

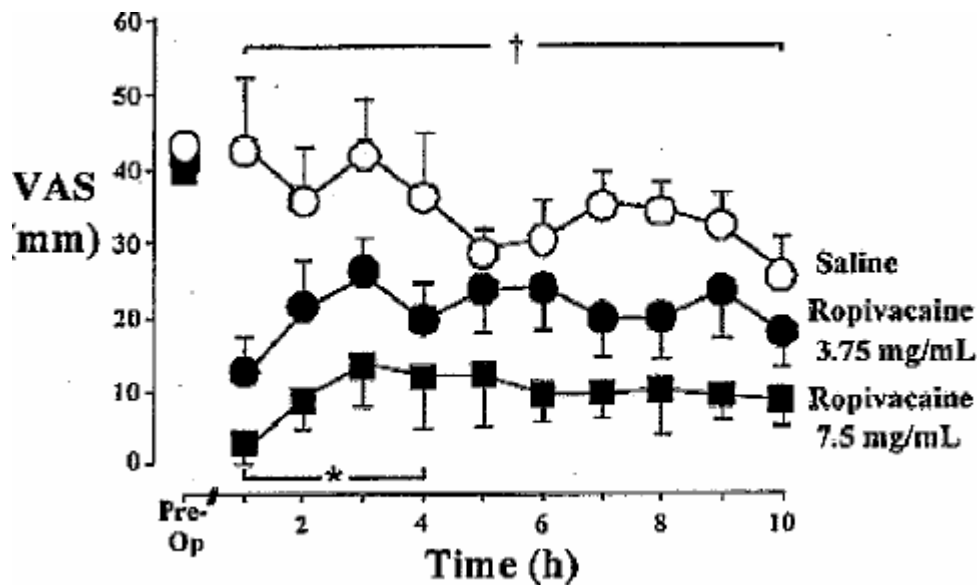


Figure 2. Preoperative pain scores were not different in the patients given ropivacaine 7.5mg/mL (40 ± 28 mm), ropivacaine 3.75mg/ml (41 ± 30 mm), or saline (43 ± 26 mm). Pain scores were significantly less during the initial 10 h postoperatively when 3.75mg/mL or 7.5 mg/mL ropivacaine was administered into the wound and surgical drain when compared with saline treated patients. Additionally, pain scores were lower during the initial 4 hours postoperatively in patients given 7.5mg/mL ropivacaine compared with 3.75mg/mL ropivacaine treated patients. $tP < 0.05$ saline versus ropivacaine treated 3.75mg/mL or 7.5 mg/mL.

* $P < 0.05$ ropivacaine 3.75mg/mL versus ropivacaine 7.5mg/mL. Data are presented as mean \pm SEM.]

With initial post-operative analgesia, the earlier and the better it is (as with a pre-infusion block or infiltration), the earlier and the better the initial mobilisation. The earlier and the better the initial mobilisation, the less the post-operative pain experienced both in severity and duration. Thus an initial block may not last 48 hours but it would be expected to have an effect on pain scores over 48 hours, compared with the placebo; whether there was a difference at 48 hours would depend on the persistence of pain in patients on placebo (with multiple factors involved such as incision site and extent).

In relation to the second point, both these infusion rates were described in the relevant summaries under efficacy. Under safety, as the sponsor acknowledges, it was pointed out that "Total exposure to the drug is not useful given that in most publications there were associated boluses, blocks or infiltrations; few had infusions of the wound only." Thus these rates at above that proposed were not mentioned a second time.

The evaluator found no reason in the sponsor's responses to modify his original evaluation.

Delegate's Comments

Based on the available evidence, the Delegate agreed with the clinical evaluator that there is evidence to justify the use of ropivacaine HCl (Naropin 0.2%) for analgesia in adults as continuous wound infusion provided that the infusion is preceded by an initial bolus dose of about 10mL ropivacaine in the proposed dosage regimen. It would appear that data were not available for children in the proposed age group (children > 12 years of age).

Regarding the nonclinical evaluator's concern, the currently approved product information for ropivacaine listed the adverse reactions pertaining to administration site conditions as 'Rare' ($\leq 0.1\%$) thereby indicating, that the potential for adverse effects on local tissues during ropivacaine continuous wound infusion would be minimally insignificant.

There is definitely no evidence to justify the proposed use of ropivacaine HCl (Naropin 0.2%) for analgesia in adults and children as intermittent wound infusion.

The Delegate proposed to recommend approval for a modified version of the proposed continuous infusion extension of indications:

Ropivacaine HCl (Naropin 0.2%) range of products (200mg/100mL and 400mg/200mL injection bags) is indicated for analgesia (Adults only) as continuous wound infusion after a pre loading 10mL bolus dose.

The Delegate proposed to reject the proposed extension of indications to use the same ropivacaine range of products for “analgesia (Adults and Children over 12 years of age) as intermittent wound infusion” due to the lack of efficacy and uncertain safety data.

The Advisory Committee on Prescription Medicines (ACPM) (formerly ADEC), having considered the evaluations and the Delegate’s overview, as well as the sponsor’s response to these documents, agreed with the Delegate’s proposal and recommended approval for the indication:

Continuous wound infusion for postoperative pain management (adults only).

In making this recommendation, the ACPM agreed with the clinical evaluator and Delegate that safety and efficacy has been demonstrated for use as continuous wound infusion. The Committee also endorsed the preloading bolus dose of 10 mL prior to continuous infusion.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration Naropin 0.2% 200mg/100ml injection bag and Naropin 400mg/200ml injection bag containing ropivacaine HCL for the new indication under Analgesia (Adults and Children over 12 years of age):

Continuous wound infusion for post operative pain management (adults only)

Attachment 1. Product Information

NAROPIN[®]

Ropivacaine Hydrochloride

PRODUCT INFORMATION

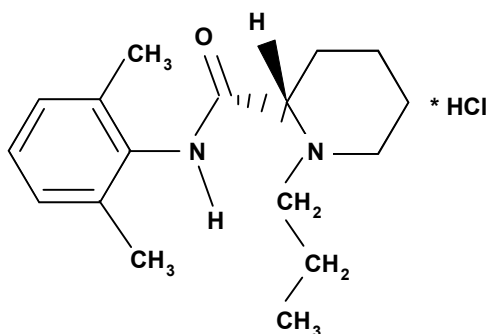
(Injection solutions for the production of local or regional anaesthesia)

NOT FOR INTRAVENOUS ADMINISTRATION UNDER ANY CIRCUMSTANCES

NAME OF THE MEDICINE

The active ingredient in NAROPIN[®] is ropivacaine hydrochloride. The CAS number for the free base is 84057-95-4. The chemical formula of ropivacaine hydrochloride is $C_{17}H_{26}N_2O \cdot HCl \cdot H_2O$.

The chemical structure of ropivacaine hydrochloride is:



DESCRIPTION

The chemical name for ropivacaine hydrochloride is (S)-(-)-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-(-)-isomer and has an enantiomeric purity of > 99%. It has a pKa of 8.1 (at 25 °C) and a molecular weight of 328.89. The pH of a saturated solution of ropivacaine hydrochloride is 4.5 and that of a 1% (w/v) aqueous solution is 5.0.

NAROPIN solution for injection is a sterile, isotonic, isobaric, aqueous solution of ropivacaine HCl in Water for Injections BP. 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. The nominal osmolality of NAROPIN 0.2% (2 mg/mL) is 288 mosmol/kg. The solution is preservative free.

The presentations of NAROPIN injection solutions are intended for single use only. Any solution remaining from an opened container should be discarded.

PHARMACOLOGY

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.

Pharmacodynamics and tolerability

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.

The peripheral neural block studies indicate that a concentration of ropivacaine of 0.5 - 1.0% consistently produces effective sensory and motor block. Neither increasing concentration above 0.75% nor adding adrenaline significantly improved the duration of motor block or anaesthesia with ropivacaine.

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 anaesthesia appeared to be 0.75 - 1.0% for ropivacaine. Duration of sensory block appeared to be comparable for equal concentrations of ropivacaine and bupivacaine.

Tests of infiltration anaesthesia in guinea-pigs showed that ropivacaine was markedly superior to bupivacaine in producing sustained cutaneous anaesthesia at all concentrations. The duration of anaesthesia produced with the least effective ropivacaine concentration (0.25%) far exceeded that produced by the highest bupivacaine concentration (0.75%).

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.

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.

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.

In man, ropivacaine is less toxic regarding the CNS and cardiovascular systems than bupivacaine. In two tolerability studies in volunteers given IV 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 a free plasma concentration of 0.34 mg/L ropivacaine and 0.13 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.

2,6-pipecoloxylidide (PPX) is an active metabolite. The threshold for systemic CNS-toxic unbound plasma concentrations of PPX in rats is about twelve times higher than that of unbound ropivacaine.

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 interactions

In preclinical studies in rats, ropivacaine interacts with agents used in conjunction with regional anaesthesia, such as benzodiazepines, thiopental, enflurane, pancuronium, suxamethonium and fentanyl, in a manner similar to that produced by the commonly used local anaesthetics bupivacaine and lignocaine. In rats, pretreatment with ropivacaine potentiated the sedative effect of morphine compared to placebo.

Pharmacodynamic drug interactions of local anaesthetics probably depend more on the physiological effects of the block, such as hypotension and bradycardia, than on circulating blood levels of the local anaesthetic.

Pharmacokinetics

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. Ropivacaine shows a biphasic absorption from the caudal epidural space also in children.

The pharmacokinetic profile of ropivacaine in adults following experimental IV administration is summarised below:

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

Ropivacaine is mainly bound to α_1 -acid glycoprotein in plasma with an unbound pharmacologically active fraction of about 6%. An increase in total plasma

concentrations during continuous postoperative epidural infusion and interscalene infusion has been observed. This increase is related to a postoperative increase of α_1 -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 approximately one twelfth of the pharmacological activity of ropivacaine. 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 unconjugated). 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 K_m (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 (see Metabolic interactions).

A similar pattern of metabolites has been found in children above one year.

Paediatrics

The pharmacokinetics of ropivacaine was characterized in a pooled population PK analysis on data in 192 children between 0 and 12 years from six studies (3 on caudals, 2 on epidural infusions, and 1 on ilioinguinal block). Unbound ropivacaine and PPX clearance and ropivacaine unbound volume of distribution initially depend on both body weight and age up to three years of age, after which they depend largely on body weight. The maturation of unbound ropivacaine clearance appears to be complete by the age of 3 years, that of PPX by the age of 1 year and unbound ropivacaine volume of distribution by the age of 2 years. The PPX unbound volume of distribution only depends on body weight.

Unbound ropivacaine clearance increases from 2.4 and 3.6 L/h/kg in the newborn and the 1-month neonate to about 8-16 L/h/kg for ages above 6 months, values within the range of those in adults. Total ropivacaine clearance values per kg body weight increase from about 0.10 and 0.15 L/h/kg in the newborn and the 1-month neonate to about 0.3 - 0.6 L/h/kg beyond the age of 6 months. Unbound

ropivacaine volume of distribution per kg body weight increases from 22 and 26 L/kg in the newborn and the 1-month neonate to 42 - 66 L/kg above 6 months. Total ropivacaine volume of distribution per kg body weight increases from 0.9 and 1.0 L/kg for the newborn and the 1-month neonate to 1.7 - 2.6 L/kg beyond the age of 6 months. The terminal half-life of ropivacaine is longer, 6 to 5 h in the newborn and the 1-month neonate compared to about 3 h in older children. The terminal half-life of PPX is also longer, from 43 and 26 h in the newborn and the 1-month old neonate to about 15 h in older children.

At 6 months, the breakpoint for change in the recommended dose rate for continuous epidural infusion, unbound ropivacaine clearance has reached 34% and unbound PPX 71% of its mature value. The systemic exposure is higher in neonates and also somewhat higher in infants between 1 to 6 months compared to older children which is related to the immaturity of their liver function. However, this is partly compensated for by the recommended 50% lower dose rate for continuous infusion in infants below 6 months.

Simulations on the sum of unbound plasma concentrations of ropivacaine and PPX, based on the PK parameters and their variance in the population analysis, indicate that for a single caudal block the recommended dose must be increased by a factor of 2.7 in the youngest group and a factor of 7.4 in the 1 to 10 year group in order for the upper prediction 90% confidence interval limit to touch the threshold for adult systemic toxicity. Corresponding factors for the continuous epidural infusion are 1.8 and 3.8 respectively.

When comparing descriptive data in a trial of caudal/epidural infusions in 10 full term neonates aged 0-30 days, to that in 18 older patients aged 31-180 days, total and unbound ropivacaine was higher and showed higher inter-individual variability, unbound apparent clearance lower and ropivacaine binding to plasma proteins (AAG) was lower. There was a greater relative excretion of ropivacaine in urine. Plasma concentrations of total and unbound PPX were similar but PPX had a longer half-life. The sum of unbound concentrations of ropivacaine and one twelfth of PPX was higher in neonates 0-7 days. While the highest level reached was 0.24 mg/L, this may have been still rising when observations ceased at 72 h (only 4 observations). The systemic CNS toxicity threshold in adults is 0.34 mg/L in a mature nervous system (see Pharmacodynamics and tolerability). It is not known how immaturity of the CNS affects toxic thresholds.

Foetuses exposed to ropivacaine during labour or Caesarean section can be regarded, after they have been born, as neonates with a peak plasma concentration at the time of delivery. The maximum unbound plasma ropivacaine concentrations in the newborn as reflected in the umbilical vein at delivery, 0.03 to 0.11 mg/L, are in the same range as those seen after single caudal block in neonates and support the documentation of ropivacaine in neonates.

Neonatal exposure based on umbilical venous plasma concentrations at delivery after epidural block for Caesarean section with ropivacaine 115 to 150 mg or continuous lumbar epidural infusion with 25 mg/h in labour.

Delivery		n	Mean	SD	Median	Min	Max
Caesarean section	C_{max} (mg/L)	71	0.33	0.16	0.30	0.11	1.12
	$C_{u, max}$ (mg/L)	69	0.07	0.02	0.07	0.03	0.11
	f_u (%)	69	21.6	6.6	22.2	6.1	34.4
Labour	C_{max} (mg/L)	10	0.32	0.13	0.34	0.13	0.52
	$C_{u, max}$ (mg/L)	10	0.05	0.01	0.04	0.03	0.07
	f_u (%)	10	16.8	8.6	12.5	8.5	30.2

Pharmacokinetics during pregnancy at term

In pregnancy at term, ropivacaine clearance is somewhat lower and its unbound clearance about half of that seen after epidural administration to non-pregnant patients. Accordingly, total C_{max} and unbound C_{max} are higher in pregnancy. The unbound plasma concentrations in the umbilical vein at delivery were similar to those in the mother and showed a fairly rapid equilibrium. There was no obvious correlation between neonatal neurologic and adaptive capacity scores and unbound or total plasma concentrations in the newborns.

Epidural Injection

Two parallel groups of 10 patients each, scheduled for epidural analgesia to relieve pain during labour, received ropivacaine or bupivacaine as a 50 mg bolus followed on request by a 25 mg top-up dose.

The unbound concentration of ropivacaine was higher than that of bupivacaine at 20 min, 0.04 (0.013) mg/L and 0.02 (0.008) mg/L as well as at 4 hours after the initial dose, 0.03 (0.006) mg/L and 0.02 (0.013) mg/L. The mean unbound fraction of ropivacaine was higher, 0.07, than that of bupivacaine, 0.04.

Epidural Infusion

Patients scheduled for epidural analgesia as pain relief during labour received a continuous lumbar epidural infusion of ropivacaine 12.5 mg/h, 25 mg/h or bupivacaine 25 mg/h after an initial dose of 12.5 mg (ropivacaine) or 25 mg (ropivacaine or bupivacaine). Treatment with ropivacaine 12.5 mg/h was terminated after 6 patients had been withdrawn due to insufficient analgesia. The results in the two groups of 10 patients each given 25 mg/h of ropivacaine or bupivacaine (2.5 mg/mL) are described below. The rate of infusion (dose) was not changed during the course of the study.

The median duration of the infusion was 6.6 hours with ropivacaine and 7.7 hours with bupivacaine, corresponding to total mean doses of 179 and 227 mg.

The maternal unbound fraction was higher after ropivacaine than after bupivacaine. The unbound plasma clearance of ropivacaine, 3.35 (1.36) L/min, was about half of that of bupivacaine, 6.40 (2.47 L/min). The mean (SD) umbilical venous unbound fraction was 0.17 (0.09) with ropivacaine and 0.12 (0.05) with bupivacaine. The unbound UV/MV ratios did not seem to increase with the duration of the infusion, indicating rapid equilibration.

Umbilical arterial (UA) and venous (UV) unbound concentrations after continuous lumbar epidural infusion of ropivacaine and bupivacaine 25 mg/h in labour are presented in the following table.

Umbilical arterial (UA) and venous (UV) unbound concentrations after continuous lumbar epidural infusion of ropivacaine and bupivacaine 25 mg/h in labour.

		UA Free (mg/L)
Ropivacaine		
Actual total dose given of ropivacaine HCl		0.027 – 0.058 (n = 4)
145 - 200 mg		
	Median	0.036
Bupivacaine		
Actual total dose given of bupivacaine HCl		0.014 – 0.021 (n = 2)
93.5 - 227.4 mg		
	Median	0.017
		UV Free (mg/L)
Ropivacaine		
Actual total dose given of ropivacaine HCl		0.027 – 0.067 (n = 10)
99.2 - 255.4 mg		
	Median	0.042
Bupivacaine		
Actual total dose given of bupivacaine HCl		0.011 - 0.035 (n = 9)
93.5 - 365.3 mg		
	Median	0.025

CLINICAL TRIALS

Adults

Two open label, randomized uncontrolled clinical studies were performed to document the efficacy and safety of NAROPIN 2 mg/mL in continuous peripheral nerve block for post-operative management up to 48 hours. In total 163 patients were studied, 136 received femoral block and 27 interscalene block. Continuous peripheral nerve blocks with NAROPIN provided effective post operative pain relief in both studies. Patient satisfaction was reported to be high.

Four open label, randomized studies were performed to investigate the efficacy and safety of NAROPIN 0.5% (5 mg/mL) and other strengths for intrathecal administration in surgical anaesthesia. A total 224 patients were studied, of which 217 patients were valid for safety and 212 for efficacy. In two studies, patients underwent minor orthopaedic, gynaecological or urological surgery suited for spinal anaesthesia. In the other two studies, patients underwent a unilateral hip replacement. NAROPIN 15 to 20 mg administered intrathecally was effective and the anaesthetic quality was rated high by surgeons, anaesthetists and patients. The incidence and severity of adverse events reported were not related to dose.

Paediatrics

A total of 5 studies, involving 246 patients aged 0-12 years, were performed to evaluate the use of NAROPIN 2 mg/mL (0.2%) for caudal block (3 studies) and continuous epidural infusion (2 studies). In the studies on caudal block, the given volumes of the ropivacaine solutions were 1 mL/kg. In one of these studies in paediatric patients between 4 and 12 years of age, three different dosages of NAROPIN (1, 2 and 3 mg/kg, 0.1%, 0.2% and 0.3%) were compared. Adequate efficacy with minimal motorblock was found for the 2 mg/kg dose. In another study on caudal block in neonates and infants between 0 and 12 months of age, the analgesic efficacy was similar to the efficacy in paediatric patients above one year of age, given the same dose per kilogram (2 mg/kg), when assessed as the proportion of patients with postoperative pain, time to first pain and time to treatment with supplementary analgesics.

In two studies in patients 1 day to 12 years old an epidural bolus was followed by a continuous infusion for up to 72 hours. The epidural bolus volume ranged between 0.5 and 1 mL/kg of ropivacaine 2 mg/mL (0.2%), with lower volumes given for thoracic than for lumbar injections. The infusion rate was 0.2 mg/kg/h in neonates and infants below 6 months of age and 0.4 mg/kg/h of ropivacaine 2 mg/mL (0.2%) in patients above 6 months of age. More than 80% of the patients had no/mild pain, or were asleep, at any time point. There was no difference in pain score between the 0 to 6 months group (ropivacaine 0.2 mg/kg/h infusion) and the 6 to 12 months group (ropivacaine 0.4 mg/kg/h infusion). The median time to supplementary analgesia was 3.3 hours in patients older than 1 year, whereas in younger patients less than 40% had been given supplementary analgesia after 72 hours. Motor block was observed in 32% of the patients above 1 year of age but in none of the infants below 1 year of age. Ropivacaine was well tolerated in all paediatric age groups.

INDICATIONS

Surgical anaesthesia (Adults and children over 12 years of age)

- epidural block for surgery including caesarean section
- intrathecal anaesthesia
- field block (minor nerve block and infiltration)
- major nerve block

Analgesia (Adults and children over 12 years of age)

- continuous epidural infusion or intermittent bolus epidural administration for analgesia in postoperative pain or labour pain
- field block (minor nerve block and infiltration)
- continuous peripheral nerve block infusion or intermittent injections for post operative pain management
- continuous wound infusion for postoperative pain management (adults only)

Analgesia (Children aged 0 - 12 years)

- Caudal epidural block in neonates (> 37 weeks gestation and over 2500 g weight), infants and children up to and including 12 years
- Continuous epidural infusion in infants (> 30 days and over 2500 g weight) and children up to and including 12 years
- Peripheral nerve block in children aged 1 up to and including 12 years

For peri- and postoperative pain management.

There are no safety or efficacy data to support the use of NAROPIN for analgesia for longer than 72 hours. (Data for peripheral nerve block administered as a continuous peripheral infusion or intermittent injections and for continuous wound infusion support the use for up to 48 hours only).

CONTRAINDICATIONS

1. Allergy or hypersensitivity to amide type local anaesthetics. Detection of suspected hypersensitivity by skin testing is of limited value.
2. Intravenous administration.
3. Local anaesthetics are contraindicated for epidural and spinal anaesthesia in patients with uncorrected hypotension.

4. 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.
5. Intravenous regional anaesthesia (Bier's block) as unintentional passage of local anaesthetic into the systemic circulation, despite the use of a tourniquet, may cause systemic toxic reactions.
6. The use of NAROPIN is not recommended for obstetric paracervical block.
7. General contraindications related to epidural anaesthesia, regardless of the local anaesthetic used, should be taken into account.

PRECAUTIONS

1. WHEN ANY LOCAL ANAESTHETIC AGENT IS USED, RESUSCITATIVE EQUIPMENT AND DRUGS, INCLUDING OXYGEN, 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 LOCAL ANAESTHETIC IS INJECTED.
2. INJECTION SHOULD ALWAYS BE MADE SLOWLY WITH FREQUENT ASPIRATIONS TO AVOID INADVERTENT INTRAVASCULAR INJECTION WHICH CAN PRODUCE TOXIC EFFECTS.
3. 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.
4. 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.
5. The lowest dosage that results in efficacious anaesthesia 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.

Children aged between 0 and 12 years should be given doses commensurate with their weight and clinical status.

6. 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 should therefore be used with caution in patients with severe hepatic disease.
7. 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 dysfunction may increase the risk of systemic toxicity (see DOSAGE AND ADMINISTRATION).
8. 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.
9. Certain local anaesthetic procedures such as injection in the head and neck region, including retrobulbar, dental and stellate ganglion blocks, may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used. The side effects may be similar to the systemic toxicity seen with unintentional intravascular injections of larger doses.
10. NAROPIN should be used with caution in patients with known drug sensitivities.
11. 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.
12. 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.

13. Major peripheral nerve blocks may involve 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. This can lead to high plasma concentrations.
14. If NAROPIN is administered simultaneously by two or more different routes, the total dose and hence the risk of systemic toxicity should be considered.
15. 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.
16. 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.
17. Neonates need special attention due to immaturity of some organs and functions. This is especially important during continuous epidural infusion. If epidural infusions are to be used in neonates, ropivacaine doses must be individually titrated by a specialist in paediatric anaesthesia. Regular monitoring for systemic toxicity (e.g. by signs of CNS toxicity, ECG, SpO₂) is always required for neonates. Monitoring should be continued after completion of infusion due to decreased rates of elimination of ropivacaine in neonates. Dose recommendations have not been established in premature neonates but organ immaturity would be expected to result in even slower elimination.
18. 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.

Carcinogenicity

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

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.

Effects on ability to drive and use machines

Depending on the dose, local anaesthetics may have a mild effect on mental function and coordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness. Patients should be warned of this possibility and advised not to drive a motor vehicle or operate machinery if affected.

Use in pregnancy – 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 NAROPIN on the developing foetus. NAROPIN should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

The epidural use of NAROPIN in obstetrics is well documented and adverse effects have been reported (see ADVERSE EFFECTS: Foetal, neonatal and infant adverse events).

Intrathecal administration has not been documented for caesarean section.

Use in 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.

Interactions with other medicines

Local anaesthetics and antiarrhythmic drugs

NAROPIN should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide type local anaesthetics, since the toxic effects are additive. Specific interaction studies with NAROPIN and class

III anti-arrhythmic drugs (e.g. amiodarone) have not been performed, but caution is advised (see PRECAUTION 15).

Adrenaline

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

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 (see Pharmacokinetics)

Ropivacaine is metabolised by the enzymes CYP1A2 and CYP3A4. Interactions with inducers of these enzymes are not expected to be clinically relevant, however there is a potential for metabolic interaction when NAROPIN is used in combination with a potent enzyme inhibitor.

CYP1A2 Inhibitors

Fluvoxamine

Oral fluvoxamine treatment caused a 70% decrease in ropivacaine clearance and a 3-fold higher AUC in healthy volunteers. Single administrations of NAROPIN should be used with care in patients who are concomitantly receiving a potent CYP1A2 inhibitor. Repeated administration or long term infusion should be avoided in such patients.

A theoretical possibility of metabolic drug interactions with potent inhibitors of CYP1A2, such as enoxacin, may exist.

CYP3A4 Inhibitors

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-hydroxy-ropivacaine but inhibited some formation of minor metabolites *in vitro*.

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 PRECAUTION 6).

Clinical relevance of interactions

In the clinical experience with NAROPIN, patients usually received NAROPIN in combination with several other therapies. The safety evaluation of NAROPIN is therefore based upon its use in combination with various concomitant treatments. The review of safety data in these studies show that NAROPIN has a safety profile comparable to other amide local anaesthetics used for regional anaesthesia.

These data did not indicate any specific drug interactions that would require special study for the use of NAROPIN as a single-dose or for treatment for less than 24 hours. Furthermore, drugs metabolised by CYP1A2, e.g. paracetamol, have also been used in combination with NAROPIN in the clinical programme, without clinical evidence of metabolic interactions (see Pharmacokinetics).

ADVERSE EFFECTS

Adverse events reported in association with NAROPIN are similar in character to those observed with other local anaesthetics of the amide type.

Adverse reactions may be due to high plasma levels as a result of excessive dosage, rapid absorption, delayed elimination or metabolism, or inadvertent intravascular injection. They should be distinguished from the physiological effects of the nerve block itself e.g. a decrease in blood pressure and bradycardia during epidural and intrathecal anaesthesia and events caused by needle puncture (e.g. spinal haematoma, postdural puncture, headache, meningitis and epidural abscess).

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.

Very common events (>10%)

Cardiovascular: Hypotension^c

Gastrointestinal: Nausea

Common events (>1%)

A large number of adverse events have been reported during clinical development, the majority related to the expected effects of the block and to the clinical situation rather than reactions to the drug. Thus hypotension and nausea have been registered in 39% and 25%, respectively, of the patients treated in clinical studies.

The following adverse events are considered to be of clinical importance regardless of causal relationship.

Cardiovascular: Bradycardia^a, hypertension and tachycardia.

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

Gastrointestinal: Vomiting^{a,d}.

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

Uncommon events (≤1%)

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

Convulsions, grand mal convulsions and seizures have been observed following unintended intravascular injection of NAROPIN.

Due to the low doses used for intrathecal anaesthesia, the potential for systemic toxic reactions is expected to be low.

Psychiatric: Anxiety

Nervous System: Hypoaesthesia^a

Vascular: Syncope^a

Respiratory, thoracic and mediastinal: Dyspnoea^a

General disorders and administration site conditions: Hypothermia^a

Rare (≤0.1%)

Cardiac disorders: Cardiac arrest, cardiac arrhythmias

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

a These reactions are more frequent after spinal anaesthesia

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

c Hypotension is less frequent in children (>1%)

d Vomiting is more frequent in children (>10%)

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 (eg, 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.

Foetal, neonatal and infant adverse events

Clinical trials have been conducted in over 400 pregnant women using NAROPIN. These studies recorded all adverse events experienced by the baby in utero, peri- or postpartum, regardless of causality to NAROPIN, other medications or other factors.

Common events (>1%)

Cardiovascular: Foetal distress, foetal tachycardia and foetal bradycardia.

Gastrointestinal: Neonatal vomiting.

Respiratory: Neonatal respiratory disorders and neonatal tachypnoea.

Other: Neonatal fever and neonatal jaundice.

Uncommon events (<1%)

Metabolic: Foetal acidosis and neonatal hypoglycaemia.

Other: Hypotonia, neonatal sepsis and low Apgar score.

DOSAGE AND ADMINISTRATION

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

The presentations of NAROPIN injection solutions are intended for single use only. Any solution remaining from an opened container should be discarded.

The lowest dosage that results in effective anaesthesia should be used and should be based on the status of the patient and the type of regional anaesthesia intended. In general, surgical anaesthesia requires the use of higher concentrations and doses than those required for analgesia.

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.

Adults and children above 12 years of age

RECOMMENDED DOSAGES FOR NAROPIN SOLUTION FOR VARIOUS ANAESTHETIC PROCEDURES IN THE AVERAGE, HEALTHY, 70KG ADULT PATIENT.

	%	Conc. mg/mL	Volume mL	Dose mg
SURGICAL ANAESTHESIA				
Lumbar Epidural Administration				
Abdominal, pelvic and lower limb surgery	0.75%	7.5	15 - 25	113 - 188
	1%	10.0	15 - 20	150 - 200
Caesarean Section	0.75%	7.5	15 - 20	113 - 150
Thoracic Epidural Administration				
Upper abdominal and thoracic surgery	0.75%	7.5	5 - 15	38 - 113
Intrathecal Anaesthesia				
Surgery	0.5%	5.0	3 - 4	15 - 20
Field Block (incl. minor nerve blocks and infiltration)				
	0.75%	7.5	1 - 25	7.5 - 188
Major Nerve Block	0.75%	7.5	10 - 40	75 - 300 ⁽¹⁾
ANALGESIA				
Lumbar Epidural Administration				
Bolus	0.2%	2.0	10 - 20	20 - 40
Intermittent injections (top-up) (e.g.) labour pain management	0.2%	2.0	10 - 15 (minimum interval 30 minutes)	20 - 30
Continuous infusion (incl. labour pain and postoperative pain management)	0.2%	2.0	6 - 14 mL/h	12 - 28 mg/h
Thoracic Epidural Administration				
Continuous infusion for postoperative pain management	0.2%	2.0	6 - 14 mL/h	12 - 28 mg/h
Field Block (incl. minor nerve blocks and infiltration)				
	0.2%	2.0	1 - 100	2 - 200
Peripheral Nerve Block (Femoral or interscalene block) Continuous infusion or intermittent injections for postoperative pain management				
	0.2%	2.0	5 - 10 mL/h	10 - 20 mg/h ⁽²⁾
Wound Infusion (adults only) Continuous infusion via surgical wound catheter for postoperative pain management ⁽³⁾				
	0.2%	2.0	4 - 10 mL/h	8 - 20 mg/h ⁽²⁾

(1) For major nerve blocks the dosage should be adjusted to the site of administration and patient status. Interscalene and supraclavicular brachial plexus blocks may be associated with higher frequency of serious

adverse reactions regardless of the local anaesthetic used.

(2) Use for up to 48 hours only.

(3) A preinfusion loading bolus dose, sufficient to fill the wound catheter and wound space is recommended. Preinfusion wound tissue infiltration should also be considered.

The appropriate concentration and volume for each procedure should be selected. The 1% (10 mg/mL) formulation is recommended for epidural anaesthesia in which a profound motor block is essential for surgery. There is no information available regarding the use of concentrations above 0.75% (7.5 mg/mL) for caesarean section. For further details of procedures please see current standard textbooks.

NOTE

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

Test Dose

For epidural anaesthesia, or when a large dose is to be injected, a 3 - 5 mL test dose of a local anaesthetic solution, preferably containing 5 µg/mL of adrenaline (e.g. 3 mL of Xylocaine® 2.0% 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 subarachnoid, 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.

Prior to and during administration of the total dose, aspiration should be repeated. The main dose should be injected **slowly** at a rate of 25 - 50 mg/min, while closely observing the patient's vital functions and maintaining verbal contact. If toxic symptoms or signs occur, the injection should be stopped immediately.

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

Analgesia

When calculating the dosage for postoperative analgesia, the use of intraoperative local anaesthetic/s should be taken into account. For treatment of postoperative pain, the following technique can be recommended:

Epidural analgesia is maintained with NAROPIN 0.2% (2 mg/mL) infusion. Infusion rates of 6 - 14 mL (12 - 28mg) per hour provide adequate analgesia with only slight and non-progressive motor block in most cases of moderate to severe postoperative pain.

With this technique a significant reduction in the need for opioids has been observed.

Clinical experience supports the use of NAROPIN 0.2% (2 mg/mL) epidural infusions for up to 72 hours. Data for peripheral nerve block administered as a continuous peripheral infusion or intermittent injections support the use for up to 48 hours only at dosages of 10 – 20 mg/hr (5 – 10 mL/hr).

When prolonged epidural 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 in adults, as were postoperative continuous epidural infusions at rates up to 28 mg/hour for 72 hours.

When prolonged peripheral nerve blocks are applied, either through continuous infusion or through repeated injections, the risk 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 0.75% (7.5 mg/mL) and interscalene block with 225 mg NAROPIN 0.75% (7.5 mg/mL), respectively, before surgery. Analgesia was then maintained with NAROPIN 0.2% (2 mg/mL). Infusion rates or intermittent injections of 10 - 20 mg per hour for 48 hours provided adequate analgesia and were well tolerated.

Use in children

Dosage Recommendations for Paediatric Patients 0 up to and including 12 Years of Age

	%	Conc. mg/mL	Volume mL/kg	Dose mg/kg
ANALGESIA				
Caudal Epidural Administration (0 – 12 years)				
Blocks below T12, in children with body weight 2.5 kg to 25 kg	0.2%	2.0	1	2
Peripheral Nerve Block (1 – 12 years) (e.g. ilioinguinal nerve block)				
	0.5%	5.0	0.4	2
Continuous Epidural Infusion (31 days – 12 years)				
In children with body weight 2.5 kg to 25 kg				
<i>31 days up to 6 months</i>				
Bolus dose ^a	0.2%	2.0	0.5 - 1	1 - 2
Infusion up to 72 hours	0.2%	2.0	0.1 mL/kg/h	0.2 mg/kg/h
<i>6 to 12 months</i>				
Bolus dose ^a	0.2%	2.0	0.5 - 1	1 - 2
Infusion up to 72 hours	0.2%	2.0	0.2 mL/kg/h	0.4 mg/kg/h

	%	Conc. mg/mL	Volume mL/kg	Dose mg/kg
<i>1 to 12 years</i>				
Bolus dose ^b	0.2%	2.0	1	2
Infusion up to 72 hours	0.2%	2.0	0.2 mL/kg/h	0.4 mg/kg/h

a Doses in the low end of the dose interval are recommended for thoracic epidural blocks while doses in the high end are recommended for lumbar or caudal epidural blocks.

b Recommended for lumbar epidural blocks. It is good practice to reduce the bolus dose for thoracic epidural analgesia.

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 and the volume for epidural bolus doses should not exceed 25 mL in any patient. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

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.

A single caudal epidural injection of NAROPIN 0.2% (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 used safely by the caudal route. The safety and efficacy of doses above 3 mg/kg have not been demonstrated and therefore cannot be recommended. The volume of the caudal epidural injection may be adjusted to achieve a different distribution to sensory block, as recommended in standard textbooks.

A single injection of NAROPIN 0.5% (5 mg/mL) at a dose of 2 mg/kg produces safe and effective analgesia when used for peripheral nerve block in children.

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

Use of NAROPIN in concentrations above 0.5% (5 mg/mL) have not been documented for children.

Intrathecal administration has not been documented for use in children.

The use of NAROPIN in premature children has not been documented.

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 local anaesthetic solution (see ADVERSE EFFECTS 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.

In children, as in adults, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during deep sedation or general anaesthesia.

After intrathecal administration, systemic toxicity is expected to be low, due to the low dose administered. However, an excessive dose administered into the intrathecal space may give rise to total spinal block.

Contact the Poisons Information Centre for advice on management of overdose.

Symptoms

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.

Treatment

If signs of acute systemic toxicity or total spinal block occur, injection of the local anaesthetic should be stopped immediately.

Treatment consists of ensuring adequate ventilation and arresting convulsions. Assisted or controlled ventilation should be maintained with oxygen, if required.

If convulsions occur and do not spontaneously stop within 15 - 20 seconds, an anticonvulsant should be given intravenously e.g. diazepam 5 - 10 mg IV 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. Children aged between 0 and 12 years should be given doses commensurate with their age, weight and clinical status.

If ventricular fibrillation, cardiac arrest or circulatory arrest occur, cardiopulmonary resuscitation must be instituted and maintained. 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.

COMPATIBILITY AND ADMIXTURES

NAROPIN solution for infusion in plastic infusion bags (Polybag) is chemically and physically compatible with fentanyl citrate, morphine sulphate and clonidine hydrochloride.

Concentration of NAROPIN: 0.1 - 0.2% (1 - 2 mg/mL)	
<i>Additive</i>	<i>Concentration</i>
Fentanyl citrate	1.0 - 10.0 microgram/mL
Morphine sulphate	20.0 - 100.0 microgram/mL
Clonidine hydrochloride	5.0 - 50.0 microgram/mL

Chemical and physical stability of these mixtures have been demonstrated for 30 days at up to 30°C. To reduce microbiological hazard, these admixtures should be used immediately. If not used immediately, store at 2 - 8°C for not more than 24 hours.

PRESENTATION AND STORAGE CONDITIONS

Naropin® 0.2% (2.0 mg/mL)

10 mL, 20 mL Polyamp DuoFit® ampoules.
100 mL, 200 mL Polybag® infusion bags.

Naropin® 0.5% (5.0 mg/mL)

10 mL, 20 mL Polyamp DuoFit® ampoules. (Not currently marketed.)

Naropin® 0.75% (7.5 mg/mL)

10 mL, 20 mL Polyamp DuoFit® ampoules.

Naropin® 1% (10.0 mg/mL)

10 mL, 20 mL Polyamp DuoFit® ampoules.

NAROPIN Polybag and Polyamp DuoFit presentations are in a Sterile AstraZeneca Theatre Pack™.

NAROPIN Polyamp presentations must be stored below 30°C. Do not freeze.

NAROPIN Polybag presentations must be stored below 30°C. Do not freeze.

Polybag and Polyamp must not be re-autoclaved.

NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription only medicine

DATE OF APPROVAL

Date of approval: 2 March 2010

Naropin, Polyamp Duofit, Polybag and Sterile AstraZeneca Theatre Pack are trade marks of the AstraZeneca group of companies.

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