CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-533/S-002

STATISTICAL REVIEW

Statistical Review and Evaluation

NDA 20-533/SE1-002
Name of drug: Naropin (ropivacaine)
Applicant: Astra
Indication: local anesthetic
Documents reviewed: volumes 1, 2, 108-175, 24 September 1998; CD-ROM copies of same
Project manager: ~~David Morgan~~ S. Samanta, M.D.
Medical officer: Monica Roberts, M.D.
Dates: received 28 September 1998, user fee goal (10 month) 28 July 1999

Reviewer: Thomas Permutt

INTRODUCTION

NDA 20-533 was approved in 1996. Ropivacaine is a local anesthetic. Chemically, it differs from the widely used drug bupivacaine in the substitution of a propyl for a butyl group, but also in being a single enanantiomer whereas bupivacaine is a racemate.

Bupivacaine carries a box warning against the use of the 0.75% (7.5 mg/mL) product in obstetrics because of reports of cardiac arrest with difficult resuscitation or death. The question of whether ropivacaine needed a similar warning was discussed by the Anesthetic and Life Support Advisory Committee before the approval of the NDA. The labeling approved in 1996 neither recommends such use nor specifically warns against it. This supplement proposes revising the labeling to recommend such use.

In January 1999 the Anesthetic and Life Support Advisory Committee met to discuss a New Drug Application for Chirocaine (levobupivacaine), a pure enantiomeric form of bupivacaine. Again, the question of the box warning was discussed. On this occasion the committee recommended not only that levobupivacaine should not carry such a warning, but that the warning be removed from the bupivacaine label if a supplement proposing this action were received.

The present supplement includes reports of clinical trials of ropivacaine 0.75% in major nerve block, cesarean section and thoracic epidural anesthesia. It also reports trials of ropivacaine 0.2% in postoperative pain, in which a higher rate and a longer duration of infusion were studied than previously. Revised labeling is proposed which describes

the new trials and recommends the newly-studied regimens. In addition, a claim is advanced that epidural ropivacaine provides better control of pain than intravenous morphine delivered by a patient-controlled pump after orthopedic surgery.

CESAREAN SECTION

Ropivacaine 0.75% was compared to bupivacaine 0.5% in four randomized, double-blind trials of epidural anesthesia for cesarean section. The supplement also reports two open-label trials. The four comparative trials M9–M12 were similar in design. The following is quoted from the report of trial M9, but very similar language appears in the other three reports:

> With the patient in the sitting or left lateral position, a test dose of 3 ml lidocaine 10 mg/ml with epinephrine 5 μg/ml was injected. Following the test dose a 3-minute interval was allowed to elapse to detect any untoward effects. A 20 ml main dose of the study-drug solution (150 mg ropivacaine or 100 mg bupivacaine) was to be injected in increments over a period of 5 minutes.
>
> Surgery was to commence when sensory block to T6, and adequate surgical anesthesia (measured by pinching with forceps within the intended area of incision) had been achieved, as judged by the investigator. Two additional 5-ml top-ups could be administered to achieve this, the first top-up dose (ropivacaine or bupivacaine) 10 minutes after administration of the main dose and, if necessary, a second 5-ml (saline in the ropivacaine group, or bupivacaine) 10 minutes later. If adequate block/anesthesia had not been obtained 40 minutes after administration of the main dose, the patient could receive other analgesics or anesthetics, at the discretion of the investigator.

Study M9 was carried out at three centers, two in Brazil and one in South Africa. Study M10 was done at eight centers in Canada. Study M11 was carried out at three centers in Norway, and study M12 was a single-center study in South Africa.

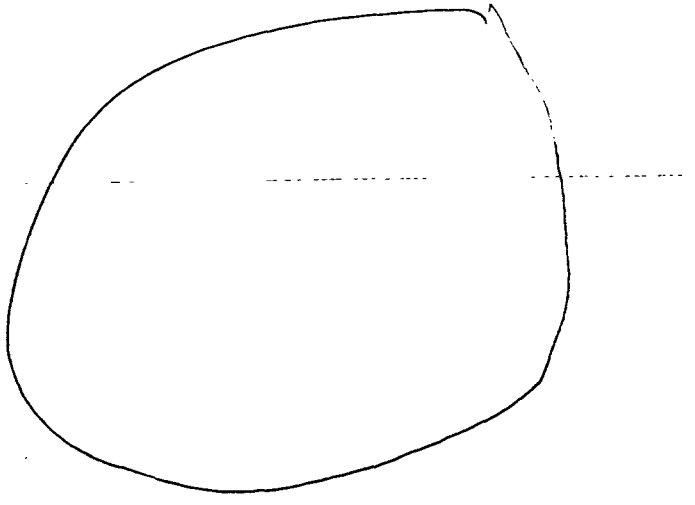
EFFICACY

Pain was assessed by the patient at several points during the procedure on a 100-point verbal scale, with zero representing no pain and 100 representing the worst pain ever. The number of patients reporting any nonzero value at delivery was prospectively specified as the primary efficacy variable. No formal analysis of equivalence was specified, and no claim of equivalence is made in the application. The fraction of patients reporting pain at delivery was numerically similar between treatments overall, and no statistically significant difference was seen in any study:

Proportion of patients with nonzero pain at delivery

	ropivacaine	bupivacaine
M9	2/52 (4%)	4/55 (7%)
M10	13/57 (23%)	15/59 (25%)
M11	4/81 (5%)	0/38 (0%)
M12	11/56 (20%)	11/59 (19%)

The proposed labeling includes descriptive statistics just for the ropivacaine group in each trial:



POTENCY

The requirement for top-ups gives some information on the relative potency of ropivacaine and bupivacaine. This is important for two reasons. First, if ropivacaine is less potent than bupivacaine, it may need to be used in higher concentrations to achieve similar results. On the other hand, ropivacaine appeared (from studies in the original NDA) to be somewhat less toxic than bupivacaine in equal doses; but if it is also less potent, then it may not be any safer in use.

Dose required (20 mg + 1 or 2 top-ups of 5 mg each)

	M9		M10		M11		M12	
dose (ml)	ropi. 0.75%	bupi. 0.5%	ropi. 0.75%	bupi. 0.5%	ropi. 0.75%	bupi. 0.5%	ropi. 0.75%	bupi. 0.5%
20	41	32	30	29	42	20	53	50
25	12	16	17	19	30	15	6	5
30	11	11	9	10	10	4	1	5

On the whole, little difference was seen between ropivacaine 0.75% and bupivacaine 0.5% in the need for top-ups. In study M9, somewhat more patients had no top-ups on ropivacaine; and in study M12, a few more patients did not need the second top-up on ropivacaine. While ropivacaine 0.75% may be slightly more potent than bupivacaine 0.5%, it is probably more like bupivacaine 0.5% than like bupivacaine 0.75%. It seems, therefore, that the higher concentration of ropivacaine may be useful in cesarean section, but any safety advantage may be lost with the higher dose.

SAFETY

No systematic differences between treatments were seen in any of the four studies in quantitative measures of likely adverse effects of local anesthetics. These included maternal blood pressure and heart rate as well as Apgar and NACS (neurologic and adaptive capacity score) measures of the condition of the newborn.

Life-threatening adverse events judged causally related (at least possibly) to study drugs were reported in one bupivacaine and three ropivacaine patients. In study M9, a ropivacaine patient had severe hypotension and fetal bradycardia; a bupivacaine patient had headache, dizziness and agitation after an accidental intravascular injection. In study M10, a ropivacaine patient had hypotension and fetal bradycardia. In study M12, a ropivacaine neonate had birth asphyxia.

Obviously, no statistical comparisons of the two treatments are called for with such small numbers of events. Rather, I call attention to these adverse experiences in connection with the question of the risk and benefit of higher concentrations of ropivacaine in cesarean section. These serious adverse events are typical of the class of drugs; their severity may be expected to be related to the concentration; and fatal events of this type have been reported with another drug of the class (bupivacaine) at higher

concentrations. This particular question of risk and benefit was avoided at the time of the original NDA because ropivacaine 0.75% was not then recommended for obstetric use; it needs to be considered carefully now.

LABELING

It is proposed to describe the studies in cesarean section as follows:

[redacted]

The six studies are the four reviewed here and two additional, uncontrolled studies. As the open-label trials do not seem to add much information, it might be preferable to refer only to the four comparative studies (*four active-controlled studies in 254 patients*).

POSTOPERATIVE PAIN

The supplement describes three kinds of trials of ropivacaine for the management of postoperative pain. In studies O13, O14 and O15 an epidural infusion of ropivacaine 0.2% was compared to intravenous delivery of morphine by a patient-controlled analgesia (PCA) device. In study O12, ropivacaine was compared to bupivacaine. In studies O10 and O11, ropivacaine was used with and without an opioid analgesic.

COMPARISON TO PCA

Three studies are submitted comparing epidural ropivacaine to PCA morphine in postoperative pain. The draft labeling claims superiority of the epidural technique.

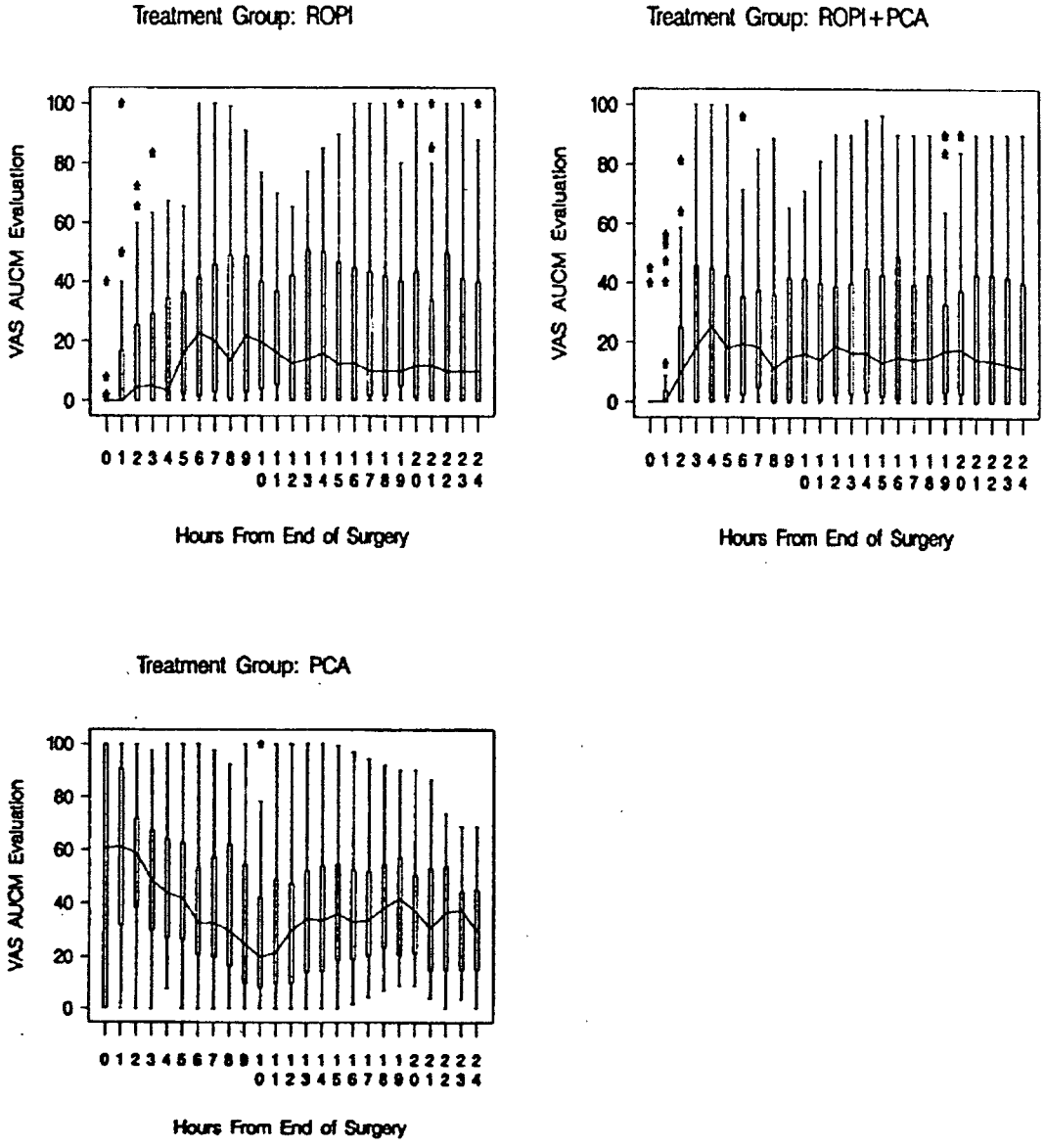
STUDY O13

Study O13 was a randomized comparison of three approaches to anesthesia and analgesia during and after total knee replacement. One hundred six patients at six centers in the U.S. were randomized in approximately equal numbers to three groups. The first group had epidural ropivacaine (1%) for surgery followed by a continuing infusion of ropivacaine 0.2% for 24 hours after surgery. The second group had the same epidural regimen as well as PCA morphine (1 mg doses with a 5-minute lockout). The third group had general anesthesia for surgery and PCA morphine afterward. The trial was not blind; given the radical differences in technique between the treatments, I believe the open-label design was appropriate.

There were eight technical failures, five in the ropivacaine group and three in the ropivacaine+PCA group. There were also two discontinuations after randomization but before administration of any study drug. Except for these 10 patients, all randomized patients had the surgery and were evaluated for post-operative pain. Patients reported pain at rest on a 100 mm visual analog scale (VAS) at intervals of one to two hours (but not between 10 p.m. and 2 a.m.)

Efficacy

The protocol specified the primary analysis unambiguously. Time-weighted averages (area under the curve) of the VAS over 24 hours were to be computed for each patient, with last observation carried forward if necessary. The three groups were to be compared by three pairwise rank-sum tests, with a Bonferroni adjustment of the significance level.



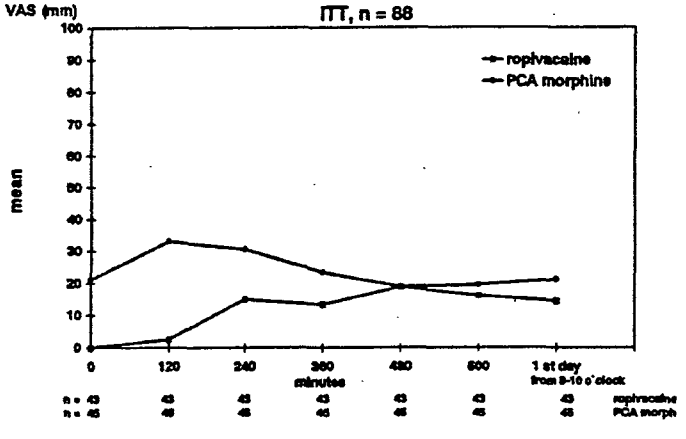
The three figures above (copied from electronic submission) show the VAS pain at rest by time for the three treatment groups. The median scores for each timepoint are connected by lines. The vertical boxes range from the 25th to the 75th percentile, and the whiskers (or the stars, in cases where the range was more than 1.5 times the interquartile range) show the whole range of data. The median 24-hour averages were 17 mm for ropivacaine, 20 mm for ropivacaine+PCA, and 39 mm for PCA. The two ropivacaine groups were statistically significantly different from the morphine group at levels 0.003 and 0.001 even after the Bonferroni adjustment. The two ropivacaine groups were not significantly different one from the other. Ropivacaine alone or in combination with PCA morphine was more effective in alleviating postoperative pain than PCA morphine alone.

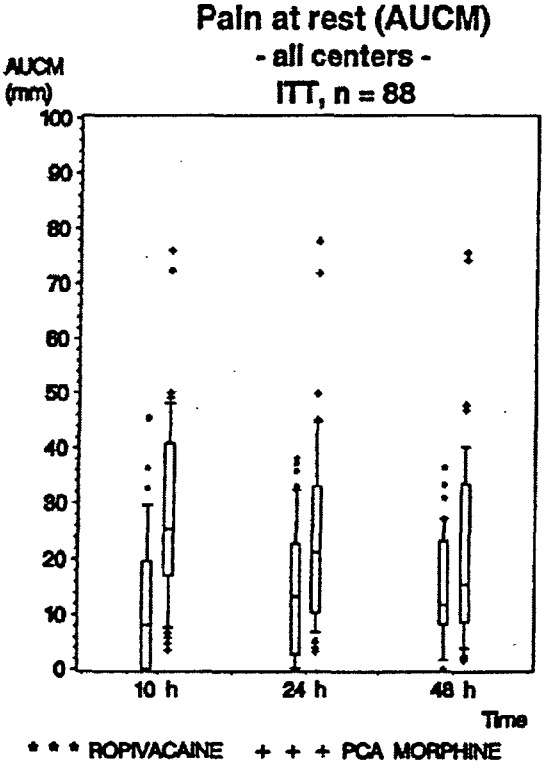
Safety

Hypotension was reported in the 24 hours after surgery in 41 percent of patients in the ropivacaine group and 68 percent in the ropivacaine+PCA group, compared to 20 percent in the PCA group. In one case in the ropivacaine group, hypotension was reported as a serious adverse event (systolic blood pressure 60 mm).

STUDY O15

Study O15 compared epidural anesthesia and postoperative analgesia with ropivacaine to general anesthesia and postoperative PCA morphine in patients undergoing total hip replacement. This time there was no ropivacaine+PCA group.



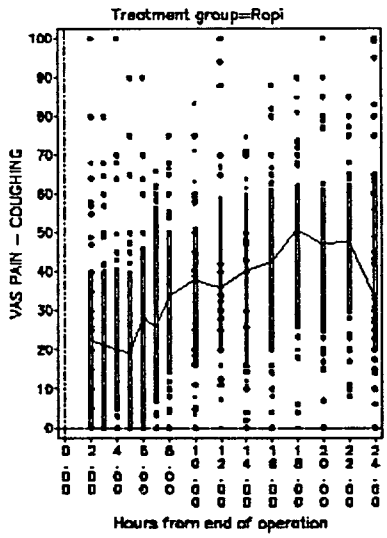


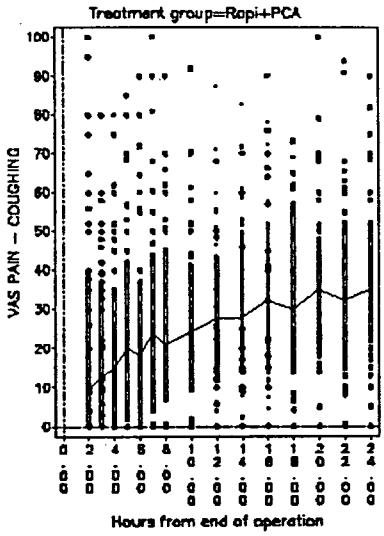
Ninety patients were randomized in approximately equal numbers to the two treatment groups at five centers in Germany. All but two patients (one technical failure with ropivacaine and one patient in the PCA group whose surgery was cancelled) were included in the intent-to-treat analysis. Again the protocol specified the 24-hour time-weighted average pain at rest as the primary outcome. The median scores were 13 mm for ropivacaine and 21 mm for PCA. The difference was significant (rank-sum test stratified by center) at the level 0.007. (Figures are copied from the submission.)

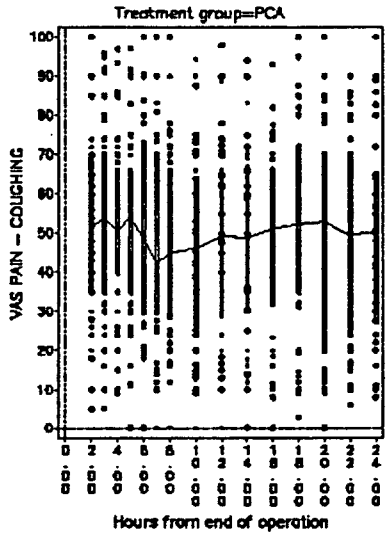
Hypotension was reported in 48 percent of the patients on ropivacaine and 30 percent on morphine. Bradycardia was reported in 32 percent on ropivacaine and 9 percent on morphine.

STUDY O14

Study O14 compared epidural ropivacaine, PCA morphine and the combination for control of pain after major abdominal surgery. In this trial all patients had general anesthesia. The ropivacaine treatment was begun after surgery, although the catheter was placed before surgery. One hundred forty-one patients were randomized at six centers in France. Eleven patients were excluded from the efficacy analysis because of discontinuation or technical failure. The primary criterion of efficacy was to be pain on coughing, averaged over 24 hours (area under the curve). Pairwise rank-sum tests with a Bonferroni







correction were specified.

The scores were significantly better in the ropivacaine and combination groups than in the PCA group, but the two ropivacaine groups were not statistically significantly different. The median 24-hour averages were 36 mm for ropivacaine, 27 mm for the combination and 50 mm for PCA alone. (The figures above are copied from the submission.)

Hypotension was again more common with ropivacaine. In the 24 hours after the end of surgery, hypotension was reported in 23 percent of the patients on ropivacaine, 38 percent on combination and 11 percent on PCA.

LABELING

The draft labeling refers to these studies as follows:

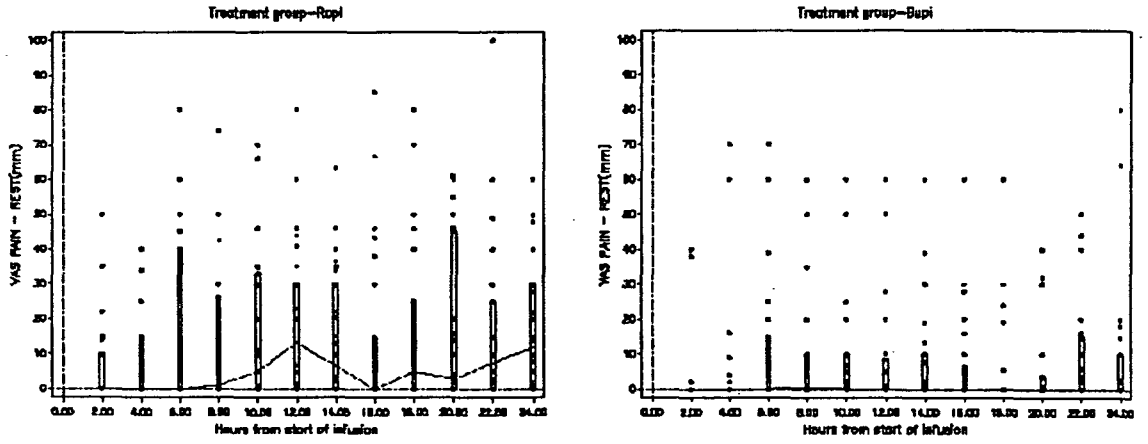
An annotation refers to studies O13 and O15, but clearly O14 is intended, as it is the only one of the three trials that studied abdominal surgery. The other study referred to is probably O13 rather than O15, as O13 was the other three-arm study.

The claim of superior pain relief versus PCA morphine is well substantiated by all three studies. The claim, if it is a claim, that PCA added to ropivacaine did not contribute to pain relief is not justified. The studies did not show that the combination was better, though there is some indication that it was better in study O14. Failing to show that it is better does not amount to showing that it is not better, however.

COMPARISON TO BUPIVACAINE (STUDY O12)

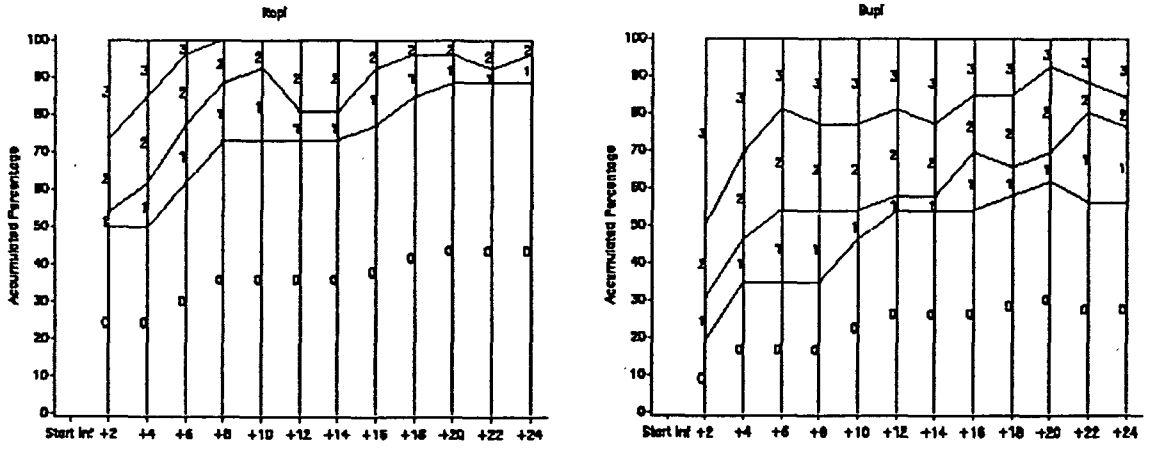
Study O12 compared ropivacaine 0.2% to bupivacaine 0.2% for the management of pain after total knee replacement. PCA morphine was also used in both treatment groups. Fifty-four patients were randomized at a single center in Northern Ireland, of whom all but two technical failures were included in the analysis population. The primary measures of outcome were 24-hour time-weighted average pain at rest on VAS and a similar average of Bromage scores of motor block. The study was evidently designed to support a claim of similar pain relief with less motor block on ropivacaine, but no formal equivalence analysis with respect to the pain scores was proposed.

The pain scores are shown on the figures (copied from the submission). The median score for bupivacaine was zero at almost all timepoints; that is, the majority of these patients reported no pain at all. The same was true of at least 25 percent of ropivacaine



patients at each timepoint, but the medians for ropivacaine were higher, and the upper quartiles were much higher. For example, a quarter of the patients on ropivacaine reported scores about 50 or higher at 20 hours after surgery, whereas no more than a quarter of the patients on bupivacaine at any timepoint reported scores above 20. In addition, the ropivacaine group used more morphine (median 31 mg) than the bupivacaine group (median 20 mg).

The motor block scores are shown below. Clearly there was less motor block of any kind as well as less of the more intense grades with ropivacaine.



The submission proposes the following labeling:

The implied claim of nearly equivalent pain relief with less motor block is not justified. The pain scores were substantially different. Thus, this study does not demonstrate better separation of analgesia from motor block with ropivacaine. Rather, it simply suggests that ropivacaine was less potent than bupivacaine at equal doses. This information about potency would be useful in the label, neutrally worded so as not to suggest an unwarranted claim:

In this study the pain scores were higher in the Naropin group, but the incidence and the intensity of motor block were lower.

WITH FENTANYL

Two studies (O10 and O11) compared epidural ropivacaine 0.2% with and without fentanyl (1, 2 or 4 µg/mL) for pain after abdominal surgery. The studies were designed primarily to determine whether the fentanyl added to the effectiveness of ropivacaine. The rate of infusion of the combination was titrated in the range of 4 to 14 mL/h. The tables, copied from the reports of studies O10 and O11, respectively, give the main efficacy data. The infusion rates were somewhat less when fentanyl was added, and the pain scores were lower, especially on coughing.

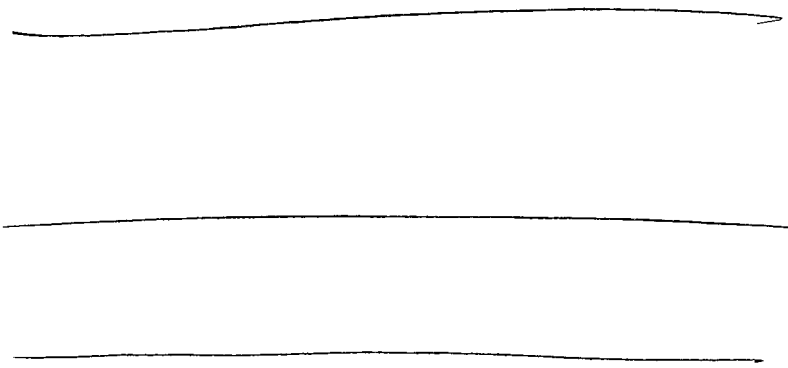
Efficacy (median)	Ropi group (n=76)	Ropi+2fent group (n=71)
Each patient's mean infusion rate 0-24 hours (ml/h)*	10.0	8.0
Each patient's mean infusion rate 0-72 hours (ml/h)*	11.5	9.3
Pain at rest AUCM** for VAS*	(n=75)	
0-24 hours	8.5	0.8
0-72 hours	9.5	3.1
Pain upon coughing AUCM** for VAS*	(n=75)	
0-24 hours	24.2	6.3
0-72 hours	22.9	9.8
Sensory block* Upper spread		
24 hours	T5	T6
72 hours	T7	T7
Lower spread*		
24 hours	L2	L2
72 hours	L1	L1

*Linear interpolation between existing values. Last value carried forward up to marked time (24 h or 72 h). **AUCM=Area under the curve divided by time.

Efficacy (median)	Ropi group (n=60)	Ropi+1fent group (n=59)	Ropi+2fent group (n=62)	Ropi+4fent group (n=63)
Each patient's mean infusion rate 0-24 hours (ml/h)*	10.2	9.8	9.5	9.3
Each patient's mean infusion rate 0-72 hours (ml/h)*	12.6	12.2	11.2	11.1
Pain at rest AUCM** (VAS)*				(n=61)
0-24 hours	8.1	7.4	4.2	3.1
0-72 hours	8.9	6.6	7.6	4.0
Pain upon coughing AUCM** (VAS)*	(n=59)		(n=61)	(n=61)
0-24 hours	18.8	18.0	15.8	7.9
0-72 hours	20.3	22.1	17.9	11.2
Sensory block* Upper spread			(n=61)	(n=62)
24 hours	T5	T5	T5	T4
72 hours	T5	T5	T6	T6
Lower spread*			(n=61)	(n=62)
24 hours	L3	L3	L2	L2
72 hours	L2	L2	L1	L1

*Linear interpolation between existing values. Last value carried forward up to marked time (24 h or 72 h). **AUCM=Area under the curve divided by time.

The application proposes the following labeling:



I do not believe this appropriately describes the studies, which were controlled trials only with respect to the use and dosage of fentanyl. The numerical information about overall adequacy of pain relief and about motor block is difficult to interpret without comparators, and seems to invite a misleading comparison to other agents. With respect to ropivacaine, the agent that would be expected to produce motor block, these are open-label, noncomparative studies. I suggest:

PERIPHERAL NERVE BLOCK

Two studies (P11 and P12) compared ropivacaine 0.75% to bupivacaine 0.5% in brachial plexus block for surgery on the arm or hand. As in obstetrics, these studies are intended to support a recommendation for use of ropivacaine at a higher concentration than originally recommended in this indication.

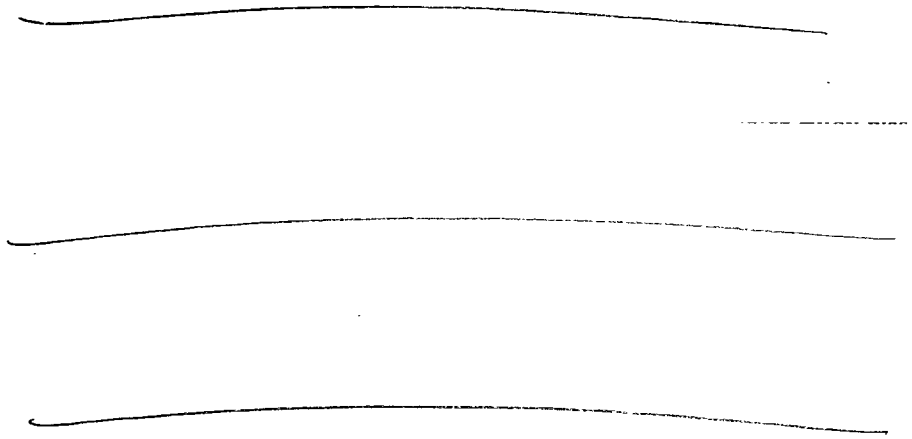
Study P11 randomized 106 patients at five centers in Canada; study P12 randomized 104 patients at five centers in Norway. In both cases the time to onset of analgesia was specified as the primary efficacy variable, and in neither case was a substantial or statistically significant difference found.

A significant difference was found in study P12 but not in study P11 in quality of analgesia and muscle relaxation. The results from study P11 are in the same direction.

Quality of analgesia and muscle relaxation, judged by anesthesiologist. Surgeons' judgments were similar. P-values from rank-sum test, by applicant.

	Study P11		Study P12	
	ropi. 0.75%	bupi. 0.5%	ropi 0.75%	bupi. 0.5%
Analgesia	p = 0.2		p = 0.0002	
excellent	33 (67%)	26 (53%)	39 (75%)	21 (43%)
satisfactory	2 (4%)	6 (12%)	11 (21%)	18 (37%)
unsatisfactory	14 (29%)	17 (35%)	2 (4%)	10 (20%)
Muscle relaxation	p = 0.5		p = 0.0004	
excellent	35 (71%)	30 (62%)	42 (81%)	24 (49%)
satisfactory	2 (4%)	4 (8%)	9 (17%)	17 (35%)
unsatisfactory	12 (24%)	14 (29%)	1 (2%)	8 (16%)

The application proposes the following labeling:



The wording is inconsistent, referring sometimes to a third study (pharmacokinetics in 14 patients) and sometimes not; the reference to the third study should be deleted. The comparative statement ("In one study the quality of analgesia and muscle relaxation in the Naropin group was judged to be significantly superior to bupivacaine by both investigator and surgeon") should explicitly mention the concentrations, lest what is partly a dose effect be mistaken for a difference between the two compounds at equal doses.

CONCLUSIONS AND RECOMMENDATIONS

The supplement reports the results of more than a dozen well-controlled clinical trials of ropivacaine in doses or techniques that are not covered by the current labeling. These new trials should be described in the product label, and I have suggested appropriate language in this review.

As the changes are substantial, however, I believe the label as a whole requires some attention regarding questions of benefit and risk. These are medical questions, and I do not make specific recommendations. They have, however, some statistical aspects, so that it is appropriate for me to call attention to them. The three main questions, all somewhat interrelated, concern, first, the safety of the 0.75% concentration of ropivacaine; second, the potency and toxicity of ropivacaine compared to bupivacaine; and, third, the separation of motor block from sensory block, again compared to bupivacaine.

Bupivacaine, the closest marketed analog to ropivacaine, carries a box warning against use of 0.75% in obstetrics. The original label for ropivacaine neither recommends nor warns against such use. The proposed label would recommend such use. On the one hand, no clear differences were seen in the reported trials between ropivacaine 0.75% and bupivacaine *0.5%*, which is recommended. On the other hand, adverse events of the kind (but not the severity) warned against were seen.

Concerning toxicity and potency, the existing labeling refers to both human and animal studies suggesting a safety benefit of ropivacaine over bupivacaine *at equal doses.* Some of the studies reported in this supplement, however, suggest that the efficacy of ropivacaine 0.75% is not very different from bupivacaine 0.5%. As the ratio of equitoxic doses is thought to be modest (less than 3:2), the impression that ropivacaine is safer at equally effective doses may be a false one.

A similar question arises with respect to motor block. In some uses of local anesthetics, especially for labor pain, blockade of sensation with minimal effect on motor function would be desirable. The existing labeling refers to motor block in some studies, and the supplement adds comments on three more. I have recommended above, for reasons specific to those studies, that this information not be included. Here, I am suggesting that all the information on motor block be considered together. It seems possible to me that there is no better separation of sensory from motor block with ropivacaine than with bupivacaine. Rather, it is possible that, when compared at equal doses, ropivacaine has somewhat less effect on both sensation and motor function. If the dose is then chosen so that sensory block is approximately complete with ropivacaine (i.e., in the top, flat part of the dose-response curve), it is difficult to see any increment in sensory block with bupivacaine. If that dose is also on the steep part of the curve for motor block, then differences might be more apparent in motor than in sensory block, even if the curves were parallel.

/S/

Thomas Permutt, Ph.D.
Mathematical Statistician (Team Leader)

/S/

Concur: Michael Welch, Ph.D.
Acting Deputy Director, Division of Biometrics II