CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-533/S-002

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

Date: October 25, 1994

CONTENTS OF APPLICATION FOR ROPIVACAINE

ITEMS 13 AND 14

PATENT INFORMATION AND CERTIFICATION

Ropivacaine is claimed in US Patent Number 4,870,086 "Optically Pure Compound and a Process for Its Preparation," expiration date September 26, 2006 and US Patent Number 4,695,576 "L-N-n-propylpipecolic acid-2,6-xylidide," expiration date September 22, 2004. The owner of these patents, ASTRA LAKEMEDEL AKTIEBOLAG (Sweden), is an affiliate of the applicant.
21 USC 355(b)(2)

In the opinion of the applicant and to the best of its knowledge, there are no other US patents which claim the drug named in this application nor which claim use of the drug for which the applicant seeks approval.
21 USC 355(b)(2)

Exclusivity Checklist

NDA: 20-533/S-002				
Trade Name: Naropin				
Generic Name: ropivacaine HCl injection				
Applicant Name: AstraZeneca LP				
Division: DACCADP (HFD-170)				
Project Manager: Kim Compton				
Approval Date:				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes		No	X
b. Is it an effectiveness supplement?	Yes	X	No	
c. If yes, what type? (SE1, SE2, etc.)	SE2			
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	X	No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes		No	X
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?				
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	X
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	X
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				
PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes	X	No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to	Yes	X	No	

produce an already approved active moiety.				
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product Naropin (ropivaccaine HCl) Injection				
NDA # 20-533				
2. Combination product.	Yes		No	X
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	X	No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes	X	No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**				
Basis for conclusion:				
b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application? * NOTE: The applicant submitted a list of published studies relevant to the safety and effectiveness of this drug product but did not submit a statement claiming that those data would not independently support approval of this application, but, we believe that the publicly available alone would not support approval of this application.	Yes	See note (*)	No	
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	X
If yes, explain:				
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored	Yes		No	X

by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?				
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #: 94-RO-83-01 (I32)				
Investigation #2, Study #: SP-ROA-0007 (P11)				
Investigation #3, Study #: SP-ROA-0008 (P12)				
Investigation #4, Study #: SP-ROA-0009 (O10)				
Investigation #5, Study #: SP-ROA-0010 (011)				
Investigation #6, Study #: 95-RO-89 (M9)				
Investigation #7, Study #: 95-RO-91 (M10)				
Investigation #8, Study #: 95-RO-96 (M11)				
Investigation #9, Study #: 96-RO-98 (M12)				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1-9	Yes		No	X
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon: Not Applicable				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1 – 9	Yes		No	X
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on: Not Applicable				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"): See item # 2 (c) above				
4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.				
a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor? NOTE: None of the studies submitted in support of this application were conducted under an IND.				
b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? NOTE: All of the studies submitted in support of this application were sponsored by Astra (AstraZeneca).				
c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	X
If yes, explain:				

Kim Compton, Regulatory Project Manager date

[S] 11/2400

Cynthia McCormick, M.D. Director date

DEBARMENT CERTIFICATION

This certifies that Astra USA, Inc. and Astra Pain Control AB, have not used and will not use in any capacity any person identified by the United States Food and Drug Administration on the recent Debarment List.

The following is a list of all relevant convictions (for which a person can be debarred) as described in section 306(a) and (b). The list covers the past five (5) years for persons employed and/or affiliated with Astra USA, Inc. and Astra Pain Control AB (including contractors) and responsible for the development of data and information to support approval of NDA 20-553 for NAROPIN® Injection (ropivacaine HCl).

Person	Date of Conviction	Charge
None	None	None

Dennis J. Bucceri
Vice President
Regulatory Affairs
Astra USA, Inc.

June 22 1998
Date

Carl-Johan Dalsgaard
President
Astra Pain Control AB

June 17 1998
Date

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETICS, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel: (301) 827-7410

MEMORANDUM

to: Division File: NDA # 20-533
DFS: NDA # 20-533 (SE2-002)

from: Cynthia McCormick, MD 151
Director, Division of Anesthetics, Critical Care and Addiction Drug Products

subject: Naropin (ropivacaine HCl injection) Efficacy Supplement Action Memo

date: September 28, 1999

This memo summarizes for the file the basis for the action to be taken on the Naropin (ropivacaine HCl injection) NDA#20-533 Supplement SE2-002 providing for multiple changes in the current approved dosage and administration of this product, an amide anesthetic indicated for regional anesthesia. The changes proposed to the current product labeling are summarized for simplicity in the table attached to this memorandum (attachment1).

The current supplement to the Naropin NDA provides for increasing the concentration of Naropin for nerve block anesthesia and lumbar and thoracic epidural anesthesia using 0.75% Naropin. Clinical studies were provided which evaluated the use of 0.75% Naropin for major nerve block, thoracic epidural administrations for cesarean section and lumbar epidural administration. This supplement is intended to extend the use of Naropin beyond the 5-mg/mL concentration for these procedures.

Second, this supplement provides for extending the duration of treatment for postoperative analgesia using 0.2% Naropin. Clinical safety studies were provided which evaluated the use of 0.2% Naropin by epidural infusion for postoperative pain management from 24 to 72 hours. There is also a proposed change in the epidural administration rate from 6-10 mL/hr to 6-14 mL/hr for lumbar administration and from 4-8 mL/hr to 6-14 mL/hr for thoracic administration. These latter studies were done with a backdrop of higher concentration and dosing intraoperatively as noted above.

Preclinical data and Biopharmaceutics data are provided in support of the new dosing recommendations.

Background

Naropin (ropivacaine HCl) is a long acting regional/local anesthetic agent (the pure s-enantiomeric form) approved in 1995. The class of drugs, the amide anesthetics are associated with characteristic CNS and cardiovascular toxicity, the focus of several meetings of the Anesthetic and Life Support Advisory Committee. The specific issue on this supplement touches on is that of toxicity of higher concentrations (and doses) particularly in the setting of epidural anesthesia for C-section. The sensitivity in this area was initiated by reports of unresuscitatable cardiac arrest due to inadvertent intravascular injection of bupivacaine (another drug in this class), usually during obstetrical epidural anesthesia. In 1983 after deliberating about the cardiovascular toxicity of bupivacaine the Anesthetics and Life Support Advisory Committee (ALSAC) made a recommendation to the FDA to undertake to assess each new local anesthetic product for very specific actions and mechanisms of action as well as specific mechanisms of toxicity. This resulted in a guidance, which was published approximately two years later which was used as a basis for the safety development program for this product.

The pivotal issue that continues to arise in the evaluation of this product is the comparative ratio for bupivacaine and ropivacaine for cardiovascular toxicity versus anesthetic potency (including motor blockade). It has been suggested that ropivacaine and bupivacaine may be comparable in the production of anesthesia, but in clinical settings where adequate motor blockade is need, higher doses of ropivacaine may be needed, thus the advantage of less apparent cardiotoxicity is lost. Cardiovascular toxicity has been demonstrated to be dose responsive in nonclinical studies of ropivacaine. The selection of 0.5% bupivacaine as an active control in the studies provided with this supplement, is probably appropriate given the assessment of the ALSAC that "Cardiac toxicity appears to be less, but not very much less, and almost equivalent to the decrease in anesthetic potency" when comparing ropivacaine with bupivacaine in the cardiovascular toxicity studies.

The studies in this supplement were recommended by the ALSAC to evaluate the safety of 0.75 % Naropin in obstetrical epidural anaesthesia and orthopedic anesthesia. In addition, several changes in the currently approved regimens, and duration of exposure were also evaluated.

Efficacy

CESAREAN SECTION

There were four active controlled trials performed in patients undergoing thoracic epidural anesthesia with 0.75% Naropin for C-section. These trials were not designed to evaluate the superiority of one agent against the other. The active control in these studies was 0.5% bupivacaine. Descriptive statistics were collected and the primary designated endpoint for these studies was absence of pain at C-section delivery. No statistical analyses were performed. The sponsor has reported % of patients reporting no pain at delivery and if a top-off dose of an additional 5-mL was needed, patients a worst case

assignment of VAS 100 was given. Comparisons between active control 0.5% bupivacaine and 0.75% Naropin showed similar success and failure. There is no basis for a comparative claim of superiority. These studies are reviewed by Dr. Hartwell and summarized and discussed by Dr. Rappaport. The active control is of some value in this setting for but a more appropriate design might have used, in addition, a dose response paradigm to compare the degree of motor and sensory block at the different doses and concentrations and to allow for a more informed analysis of risk to benefit at the higher concentration (and dose). Since the current approved label allows for the administration of 0.5% Naropin (dose not specified) in the setting of C-section, it would have been of greater value to compare new doses and concentrations to the approved regimen.

MAJOR NERVE BLOCK (BRACHIAL PLEXUS)

Efficacy in brachial plexus block was evaluated in two double blind active controlled, parallel design studies using 0.75% Naropin and 0.5% bupivacaine. Study P11 (which studied 0.75% Naropin at a dose of 225 mg administered by subclavian approach) and Study P12 (0.75% Naropin at a dose of 300 mg administered by axillary approach) both demonstrated effective blockade by either agent on the prospectively defined outcome measures. No superiority of one agent over the other could be demonstrated using the primary outcome measure—onset of analgesia in five nerves of the plexus. When "quality of anesthesia" is compared, however, the findings in study P12 suggested that 0.75% Naropin is more effective than bupivacaine 0.5% when used for an axillary brachial plexus block, in doses of 300 mg. This was not replicated, but if it had been a positive effect it would have to be weighed against the adverse effects as described below. Without confirmation of these findings, no claims of superiority should be granted.

POSTOPERATIVE PAIN

Postoperative pain has been evaluated in 4 controlled studies, some of which were preceded by intraoperative epidural blockade. Dr. Rappapport has discussed these and no additional issues are apparent.

Lumbar epidural anesthesia has been discussed by Dr. Rappaport and presents no additional issues. Efficacy is adequately supported in the higher concentration.

Biopharmaceutics

Eight clinical /pharmacokinetics studies involving 119 subjects were submitted in support of the new dosing extensions. The only significant finding in all of these studies was that patients undergoing major nerve block (brachial plexus) with 0.75% Naropin in doses approaching 300-375 mg had plasma concentrations approaching the threshold reportedly associated with CNS toxicity. This was evaluated in the analysis of the pooled safety data in this group.

No significant issue was apparent in the pharmacokinetics of 0.75% ropivacaine in pregnant patients undergoing cesarean delivery, dosed in the range of 150-187.5 mg. It

was found that unbound ropivacaine appears to increase dose-proportionally between 150 and 187.5 mg administered in this population. Bioavailability was comparable between 0.5% and 0.75% Naropin used in epidural block in cesarean patients. It was found that ropivacaine is distributed to the fetus, based on plasma concentrations in UA/UV ratios (consistently about 0.8). This was considered in the analysis of the pooled safety data, particularly in the neonatal assessments, of the cesarean section studies.

Safety—Nonclinical

Preclinical reproductive toxicology studies were performed in to support the higher concentration of Naropin in patients undergoing C-section delivery. These included cardiovascular toxicity studies in addition to those already reviewed at the time of the NDA submission. As Dr. Goheer reports in his review, at high IV doses, ropivacaine has cardiovascular toxicity similar to that of bupivacaine. The doses that produced hypotension, respiratory arrest, or circulatory collapse were also shown to be similar in pregnant and nonpregnant ewes given IV ropivacaine. Studies on the treatment of acute toxicity resulting from rapid IV administration of ropivacaine and bupivacaine in conscious dogs (summarized on p. 69 of Dr.Goheer's review) and even though no fatalities were reported in the ropivacaine dogs and two of the bupivacaine animals could not be resuscitated, the study showed no statistically significant difference between the survival of dogs who developed cardiac toxicity after receiving doses exceeding the convulsive doses of bupivacaine and ropivacaine. This unresolved question or resuscitatability should be both pursued by an adequately powered study and qualified in the package insert.

Safety—Clinical

The following table summarizes the exposures by dose, duration, and concentration found in this supplement. It reflects also the manner in which safety data were pooled in order to assess each proposed change in the labeling.

	Conc.	Duration	Dose (range) mean	N
Cesarian Section *Lumbar epidural*	.75%	Single dose	164 (150-189)	324
Brachial Plexus Block	.75%	Single dose	263(225-300)	119
Postoperative Pain:				
Thoracic epidural (014,)	.2%	72 hrs	1449 (566-1999) (6-14 mL/hr)	173
Lumbar epidural (013,015)	.2%	72 hr infus	1235 (107-2129) (6-14 mL/hr)	141
Lumbar epidural	.2%	72 hr infus	1266 mg(38-2236`) (6-14 mL/hr)	116
Lumbar epidural	.2%	72 hr infus	1049 (490-1409) (6-14 mL/hr)	11

CESAREAN SECTION

The safety of 0.75% Naropin was evaluated in 324 women undergoing cesarean section[1]. The breakdown of exposure by dose is recorded in the following chart, which shows the majority of dosing in the 150-mg dose group. In these studies, patients receiving 0.75% Naropin were compared with patients receiving 0.5% bupivacaine (higher concentration bears prominent warnings in the label) rather than to the approved Naropin regimen. Safety was evaluated both in terms of maternal factors and neonatal outcomes, specifically, fetal monitoring (before delivery) and Apgars, NAC assessments and umbilical venous pH. The maternal adverse events were collected and as expected from high thoracic epidural anesthesia, included hypotension and nausea. The incidence of adverse events was comparable between groups. Adverse events in neonates were reported with similar incidence.

Clinical studies, then, including more patients undergoing C-section with 0.75% Naropin anesthesia than even in the original NDA for which 0.5% Naropin was approved, did not reveal any significant concerns. The total safety database in this higher dose and

[1] The only previous data provided for dosing in this range was in the original NDA submission, in an open label study in which 7 women received 0.5% ropivacaine and 32 received 0.75% ropivacaine, both in the range of 150 mg by a high thoracic epidural administration for C-section. The study did not provide sufficient safety data for comparison.

concentration, including the exposures from the NDA are 356 patients. This should be sufficient to disclose adverse events occurring with an incidence of greater than 0.3%.

The central question remains that of the potential serious cardiovascular toxicity in the event of accidental intravascular injection of Naropin given in higher concentrations and higher doses. It was pointed out at a recent meeting of the ALSAC which discussed this same issue with another agent, that there are new standards for regional anesthesia practice in obstetrics, such as giving incremental boluses, and immediate availability of resuscitative equipment, use of multiorifice[2] catheters, which mitigate against the likelihood of this kind of serious event occurring. Taken together with the preclinical and clinical results, and with appropriate warnings in the label, it appears that the sponsor has done everything reasonable and appropriate to evaluate the safety of this concentration and dose in patients undergoing C-section delivery.

Table: Exposure by dose in patients receiving 0.75% Naropin for C-section

150 mg	*165 mg*	*187.5 mg*	*225 mg*
212	1	103	8

MAJOR NERVE BLOCK (BRACHIAL PLEXUS)

Three studies involving brachial plexus block were provided in this supplement in support of administration of a higher concentration (0.75%). The lower concentrations had been previously approved, but based on the need for readministration of drug (alluded to at ALSAC 12/95) the 0.75% concentration was thought to be needed. The sponsor studied 0.75% Naropin against 0.5% bupivacaine but did not compare the safety of .75% with 0.5% Naropin. A total of 119 patients received doses of 0.75% Naropin ranging from 225 to 300 mg. A single pharmacokinetics study of 0.75% naropin administered for brachial plexus block in three dose groups revealed that when doses approach 300 mg (40 mL) the plasma levels approach the threshold reported for CNS toxicity. Review of the adverse event profile in this pooled safety dataset demonstrated a dose response for CNS adverse events only. Dizziness was reported in (0/54) 0% of patients receiving 225 mg (30mL), (0/2) 0% of patients receiving 265 mg (35 mL) and (6/52) 10% of patients receiving 300 mg (40 mL). In addition, one patient receiving 300 mg of 0.75% Naropin developed slurred speech followed by a grand mal seizure. The serious adverse event was attributed to accidental intravascular injection, however this was purely speculative. One patient in the control group also had a seizure reported. The characteristics of this class of drug makes it plausible that the seizures were due to the drug. The safety of the higher concentration of Naropin is supported in this supplement with cautionary labeling to reflect these findings at the higher doses.

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[2] Two recent studies by Norris et al in St. Louis have shown that aspiration of a multiorifice catheter has a greater than 99.5% chance of reliably detecting intravascular placement just on aspiration.

Lumbar epidural anesthesia has been discussed by Dr. Rappaport and presents no additional issues. Safety is adequately supported in the higher concentration.

POSTOPERATIVE PAIN

The safety of Naropin 0.2% by lumbar or thoracic epidural continuous infusion was assessed over a 72-hour period in the treatment of postoperative pain. As Dr. Rappaport points out in his supervisory review, the adverse events reported in the continuous infusion studies of epidural 0.2% Naropin alone or in combination with opiates revealed no clinically unexpected events and no increase in the incidence of serious adverse events as a function of time. I concur with the review team that the safety of 0.2% Naropin for up to 72 hours continuous infusion is supported by this pooled database of 441 patients undergoing continuous epidural infusion for postoperative pain. The increase in infusion rate (the higher dose) is similarly supported.

Recommended Action: Approvable for

(1) use of Naropin 0.75% in doses not exceeding 300 mg (40 mL) for brachial plexus blockade
(2) use of Naropin 0.75% for use in Cesarean section in doses not to exceed 187.5 mg.
(3) use of Naropin 0.2% for up to 72 hours infusion for treatment of postoperative pain.

The changes in the labeling (attached) will be negotiated with the sponsor.

ATTTACHMENT 1

Summary of Proposed Changes to Label

Indication	Current	Proposed
Postoperative Pain		
Δ duration and rate	2 mg/ml x 24 hours duration	2 mg/ml x 72 hours duration
for lumbar epidural administration)	rate 6-10 ml/hr	rate 6-14 ml/hr
for thoracic epidural administration)	rate 4-8 ml/hr	rate 6-14 ml/hr
Epidural Anesthesia		
Δ concentration Cesarean section –thoracic epidural administration	5mg/mL	7.5mg/mL
Other—lumbar epidural administration	5mg/mL	7.5mg/mL
Major Nerve Block		
Δ concentration		
Epineural (Brachial Plexus)	2 mg/ml	7.5 mg/mL

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

MEMORANDUM

DATE: November 2, 2000

TO: File, NDA 20-533

FROM: Bob A. Rappaport, M.D.
Deputy Director, DACCADP
Team Leader, Anesthetic Drug Group

THROUGH: Cynthia G. McCormick, M.D.
Director, DACCADP

RE: NDA 20-533 SE2-002, Response to Approvable Letter, for Naropin (ropivacaine HCl) Injection Action Memo

BACKGROUND:

NDA 20-533 SE2-002 was originally submitted by ASTRA USA on September 28, 1998. The supplement purportedly provided evidence for the safety and efficacy of:

1. "...increasing the dosage for nerve block anesthesia using Naropin 7.5 mg/mL...for major nerve block (e.g. brachial plexus block), lumbar epidural administration for cesarean section and for thoracic epidural administration. Our current labeling only allows for Naropin 5 mg/mL to be used in these procedures."

2. "...extending the duration of treatment for postoperative analgesia using Naropin 2 mg/mL... for postoperative pain management from 24 hours to 72 hours."

3. " [increasing] The epidural infusion rate for postoperative pain management...for lumbar administration from 6-10 mL/h to 6-14 mL/h and for thoracic administration from 4-8 mL/h to 6-14 mL/h."

Based on a thorough review of the data submitted in the supplementary application, an Approvable Letter was issued on September 28, 1999. The letter stated that the application was approvable and that this approval would be based on the submission of draft labeling revised as indicated by the Agency. As per standard practice, a safety update was requested at the time of response to the approvable action.

On May 2, 2000, a complete response to the Approvable Letter was submitted. That submission included the requested safety update and revised labeling. The updated safety database is discussed in Dr. Patricia Hartwell's clinical safety review dated October 30, 2000. Dr. Hartwell found no new safety concerns raised by the findings in the enlarged database compared to the original database for the supplement.

The complete response also contained new efficacy and safety data in the form of four newly completed studies. The sponsor was informed that the effectiveness data from these four studies had been inappropriately submitted with this response document; and that it would not be reviewed as an element of this supplement. The sponsor agreed to resubmit these four studies as a new supplement.

As addressed in Dr. McCormick's original Action Memo for this supplement, the Division's concerns regarding the new indication for the use of 0.75% Naropin in obstetrical patients were adequately allayed by the increased safety database for that population submitted as part of the original supplementary application.

Minor revisions to the resubmitted labeling were sent to the sponsor for review. Agreement was reached between the sponsor and the Division on the wording for the revised label.

ACTION

This application is approved with the attached labeling.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

MEMORANDUM

DATE: September 21, 1999

TO: File, NDA 20-533

FROM: Bob A. Rappaport, M.D.
Deputy Director, DACCADP
Team Leader, Anesthetic Drug Group

RE: Supervisory Review of NDA 20-533, S-002
Naropin (Ropivacaine HCl Injectable)

BACKGROUND:

ASTRA USA submitted NDA 20-533 S-002 for Naropin (Ropivacaine HCl Injectable) on September 28, 1998. The original NDA for Naropin was approved on September 24, 1996. That application included 2.0, 5.0 and 10.0 mg/mL concentrations of ropivacaine indicated for local and regional anesthesia for surgery for postoperative pain management and for obstetrical procedures. Prior to the approval, the Anesthetics and Life Support Advisory Committee (ALSAC) was convened to address concerns of cardiac toxicity of 0.75% ropivacaine when used for epidural block for Cesarean section. A recommendation was made that additional clinical trials be performed in order to better assess the safety profile of the 0.75% concentration's safety profile in the Cesarean section setting.

The cover letter to this supplement notes that it provides evidence for the safety and efficacy of:

1. "...increasing the dosage for nerve block anesthesia using Naropin 7.5 mg/mL...for major nerve block (e.g. brachial plexus block), lumbar epidural administration for cesarean section and for thoracic epidural administration.

Our current labeling only allows for Naropin 5 mg/mL to be used in these procedures."

2. "...extending the duration of treatment for postoperative analgesia using Naropin 2 mg/mL... for postoperative pain management from 24 hours to 72 hours."

3. " [increasing] The epidural infusion rate for postoperative pain management...for lumbar administration from 6-10 mL/h to 6-14 mL/h and for thoracic administration from 4-8 mL/h to 6-14 mL/h."

This supplement includes information from 20 clinical trials, 10 of which were, in some form, controlled. A total of 1991 patients were treated in the controlled trials and 59 in the uncontrolled studies.

The clinical studies of the effectiveness and safety of this new product have been reviewed by Monica Roberts, M.D and Patricia Hartwell, M.D. Thomas Permutt, Ph.D. (biostatistics), Shinja Kim, Ph.D. (clinical pharmacology and biopharmaceutics), and Anwar Goheer, Ph.D. have also reviewed the application. (pharmacology/toxicology). In this memo, I will briefly review the effectiveness and safety data summarized in the primary clinical review, as well as any relevant information found in the primary reviews from the other disciplines, and make appropriate recommendations for action on the NDA.

EFFECTIVENESS:

Evidence of effectiveness has been submitted in 10 clinical trials. One trial [94RO85 (O12)] compared 2 mg/mL ropivacaine to 2 mg/mL bupivacaine by continuous epidural infusion for postoperative pain management. Three trials [SP-ROA-0010 (O13); SP-ROA-0010 (O14); and SP-ROA-0010 (O15)] compared ropivacaine 2 mg/mL (following an intraoperative bolus of ropivacaine 20 mL of 2 mg/mL or 10 to 15 mL of 10 mg/mL) to PCA morphine for postoperative pain management. (Trials O13 and O14 included a third arm of epidural ropivacaine plus PCA morphine.) Two trials [SP-ROA-007 (P11); and SP-ROA-0008 (P12)] compared ropivacaine 7.5 mg/mL to bupivacaine 5 mg/mL via brachial plexus block for upper extremity surgery. Four trials [95RO89 (M09); 95RO91 (M10); 95RO96 (M11); and 95RO98 (M12)] compared ropivacaine 7.5 mg/mL to bupivacaine 5 mg/mL administered as epidural block for Cesarean section.

In addition, evidence of effectiveness has been submitted in a number of supportive clinical studies. Studies SP-ROA-0009 (O10) and SP-ROA-0010 (O11) compared epidural ropivacaine alone to epidural ropivacaine plus fentanyl for postoperative pain management. These studies did not examine the efficacy of ropivacaine by use of a comparator and are, thus, only useful as supportive data. Studies 94RO83-01 (I32) and

94RO84 (O9) were small pharmacokinetic studies supportive of efficacy for ropivacaine when used as epidural block and continuous infusion for postoperative pain management.

Studies 91RO47 (M04) and 94RO80 (M08) were small, open label evaluations of the efficacy of ropivacaine 7.5 mg/mL for epidural block during Cesarean section. Finally, the sponsor submitted four adequate and well-controlled studies of ropivacaine 7.5 mg/mL compared to bupivacaine 2.5 mg/mL or placebo administered as infiltration nerve block for postoperative pain management. However, as the sponsor has not requested that these four studies be used in support of a new claim of effectiveness, they have been reviewed only in brief.

POST-OPERATIVE PAIN STUDIES:

Study 94RO85 (O12):

This was a randomized, double blind, parallel group study comparing 2mg/mL ropivacaine to 2-mg/mL bupivacaine administered by continuous epidural infusion in patients recovering from total knee replacement. The study was performed at one center.

Patients were randomized to one of the two treatment arms, either 2mg/mL ropivacaine or 2-mg/mL bupivacaine via epidural catheter. Preoperative medications included tamezepam or midazolam and prophylaxis for thrombosis. All patients received at least one liter of crystalloid or crystalloid colloid mixture. Patients underwent epidural block (with one of the two study drugs) to T10 followed by surgery under general anesthesia induced with propofol, atracurium and fentanyl (maximum dose = 200 μg) and maintained with isoflurane, nitrous oxide/oxygen, atracurium and fentanyl (50 μg as needed). Within 30 minutes of the end of surgery, an infusion of ropivacaine or bupivacaine (the same drug used for the surgical block) was started and maintained at a constant rate of 8 mL/hour for 24 hours. Neuromuscular blockade was reversed with neostigmine and glycopyrrolate. When the patient was fully awake, a PCA pump was connected which delivered 1.0 mg boluses of morphine with a 5 minute lockout period. Additional doses of morphine were administered at the discretion of the investigator.

The primary measures of efficacy were the AUCM24's[1], areas under the curve at 24 hours, based on VAS (Visual Analogue Scale of 100 mm) measurements for pain at rest and a modified Bromage score measurement of motor function.

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[1] The area under the curve, based on repeated measurements up to 24 hours, was calculated using the trapezoidal rule, extended to the 24-hour point by extrapolation if necessary. The summary measure was defined as this area under the curve divided by the length of the time period on which it was based, so that it had the same scale as the underlying repeated measurements. The summary measure was denoted AUCM24.

Secondary efficacy measures included:

1) AUCM scores for pain at rest at the time intervals: 0-4 hours and 0-8 hours;
2) VAS pain at rest scores
3) VAS pain at rest scores equal to or greater than 30 mm for time intervals: 0-4 hours, 0-8 hours, and 0-24 hours;
4) VAS scores for pain during mobilization
5) VAS pain during mobilization scores equal to or greater than 30 mm for time intervals: 0-4 hours, 0-8 hours, and 0-24 hours;
6) AUCM scores for pain during mobilization at the time intervals: 0-4 hours, 0-8 hours, and 0-24 hours;
7) Spread of sensory block;
8) AUCM scores for number of blocked dermatomes;
9) Motor block for the non-operated leg;
10) AUCM scores for motor block in the non-operated leg at the time intervals: 0-4 hours and 0-8 hours;
11) Return of normal motor and sensory function;
12) Morphine consumption; and
13) Quality of pain relief.

Results:

A total of 54 patients were enrolled in the study, 28 randomized to the ropivacaine group and 26 to the bupivacaine group. Two patients in the ropivacaine group were withdrawn from the ITT group (one due to intravascular injection of study drug and the other intravenous injection of the test dose of lidocaine). Twenty-six patients in each group comprised the ITT. One patient in the bupivacaine group was withdrawn (after 20.5 hours of infusion) from the per protocol [PP] analyses due to confusion and inability to give accurate answers to study assessments.

Treatment groups appeared to be generally matched on relevant measures at baseline.

Primary Efficacy Analyses:

At 0-24 hours there was a statistically significantly higher AUCM score in the ropivacaine group (14.29) compared to the bupivacaine group (7.42), p=0.017.

At 0-24 hours, the ropivacaine treated patients had a lower degree of motor block (0.50 ± 0.56) in the non-operated leg than the bupivacaine treated patients (1.16 ± 1.00), p=0.015.

Secondary Efficacy Measures:

AUCM scores for pain at rest at the time intervals: 0-4 hours and 0-8 hours:

The mean AUCM scores for pain at rest at 0-4 hours were 6.70 for ropivacaine and 3.86 for bupivacaine. The mean AUCM scores for pain at rest at 0-8 hours were 10.78 for ropivacaine and 6.51 for bupivacaine. Neither of these differences was statistically significant.

VAS pain at rest scores:

No statistical analyses were performed. However, per Dr. Permutt's review, page 10, the median scores for the ropivacaine group were higher and the upper quartiles were much higher than the bupivacaine group.

VAS pain at rest scores equal to or greater than 30 mm for time intervals: 0-4 hours, 0-8 hours, and 0-24 hours:

For the time interval 0-24 hours, there was a statistically significantly higher number of patients in the ropivacaine group with a pain score at rest ≥30 mm, p=0.028. For the intervals 0-4 and 0-8 hours, there were no statistically significant differences were noted between the ropivacaine and bupivacaine treated patients. [See Dr. Roberts' Table 6, page 31 of the medical review, for actual scores]

VAS scores for pain during mobilization:

Pain scores during mobilization were generally higher in the ropivacaine group than the bupivacaine group. The median scores varied over time ranging from 0 to 40 mm in the ropivacaine group and 0 to 16 in the bupivacaine group. No actual statistical analysis was performed.

VAS pain during mobilization scores equal to or greater than 30 mm for time intervals: 0-4 hours, 0-8 hours, and 0-24 hours:

For the time interval 0-24 hours, there was a statistically significantly higher number of patients in the ropivacaine group with a pain score during mobilization ≥30 mm, p=0.040. For the intervals 0-4 and 0-8 hours, there were no statistically significant differences were noted between the ropivacaine and bupivacaine treated patients. [See Dr. Roberts' Table 7, page 33 of the medical review, for actual scores]

AUCM scores for pain during mobilization at the time intervals: 0-4 hours, 0-8 hours, and 0-24 hours:

At 0-24 hours there was a statistically significantly higher AUCM score for pain during mobilization in the ropivacaine group (27.02) compared to the bupivacaine group (16.25), p=0.016. For the intervals 0-4 and 0-8 hours there were no statistically significant differences between the two groups.

Spread of sensory block:

The spread of sensory block was similar in both groups. No actual statistical analysis was performed. [see Dr. Roberts' discussion, page 39 of the medical review]

AUCM scores for number of blocked dermatomes:

For the time intervals 0-4 hours and 0-8 hours there were statistically significantly lower AUCM scores for the ropivacaine group compared to the bupivacaine group for number of blocked dermatomes (p=0.016 and p=0.037, respectively). At 0-24 hours there was no statistically significant difference between the two groups. [see Dr. Roberts' Table 9, page 37 of the medical review, for actual numbers]

Motor block for the non-operated leg:

Two hours after surgery, 50% of the ropivacaine treated patients and 19% of the bupivacaine treated patients had no motor block. Twenty-four hours after surgery, 88% of the ropivacaine treated patients and 56% of the bupivacaine treated patients did not have motor block. No statistical analysis was performed.

AUCM scores for motor block in the non-operated leg at the time intervals: 0-4 hours and 0-8 hours:

At both time intervals the ropivacaine treated patients had a lower degree of motor block in the non-operated leg than the bupivacaine treated patients, p=0.041 and 0.022, respectively. [see Dr. Roberts' Table 10, page 39 of the medical review for actual numbers]

Return of normal motor and sensory function:

Return of normal motor function in the non-operated leg occurred at 4 hours after the infusion was discontinued for the ropivacaine group and 5 hours for the bupivacaine group. Return of normal sensory function occurred at 5 hours after the infusion was discontinued for 100% of the ropivacaine treated patients and at 6 hours for 96% of the bupivacaine treated patients. No statistical analyses were performed.

Morphine consumption:

The median consumption of morphine was 30.7 mg for the ropivacaine treated patients and 20.5 mg for the bupivacaine treated patients. No statistical analysis was performed.

Quality of pain relief:

The overall quality of pain relief was rated as good or excellent in 77% of the ropivacaine treated patients and 80% of the bupivacaine treated patients. This difference was not statistically significantly different.

Comments:

Bupivacaine 2 mg/mL at a constant infusion rate of 8 mL/hour over 24 hours appeared to provide consistently better pain control than ropivacaine 2 mg/mL at the same infusion rate. While ropivacaine did appear to result in less significant motor block during the infusion and the recovery period, this would be expected with the significantly lower potency of ropivacaine in this setting, documented by its lesser ability to control pain than an equivalent dose of bupivacaine.

Study SP-ROA-0010 (O13):

This was a multicenter, randomized, open-label, parallel group performed in Australia and New Zealand. Patients were randomized to one of the three treatment arms prior to surgery for total knee replacement:

1. Epidural ropivacaine for surgery followed by continuous epidural ropivacaine for postoperative pain management;
2. Epidural ropivacaine for surgery followed by continuous epidural ropivacaine and PCA morphine for postoperative pain management; or
3. General anesthesia for surgery followed by PCA morphine for postoperative pain management.

Patients were premedicated with midazolam and fentanyl was administered at the discretion of the investigator. Patients also received prophylaxis for thrombosis, antiemetics and crystalloid infusion. For the patients in the two epidural ropivacaine groups, the maximum allowed dosages were: 5 mg midazolam, 250 µg fentanyl and 200 mg propofol. No antiemetic was allowed for these two groups. Additional 10 mL doses of 10 mg/mL ropivacaine (100 mg) were allowed before or during surgery at the discretion of the investigator. If adequate sensory block was not achieved within 45 minutes of the initial injection of the primary dose, the patient was discontinued from the efficacy assessments.

For the patients who received general anesthesia, the following medications were allowed:

Induction and muscle relaxation:	thiopental/propofol atracurium/vecuronium/succinylcholine/pancuronium fentanyl
Maintenance:	isoflurane/nitrous oxide:oxygen/air:oxygen atracurium/vecuronium/suxamethonium/ pancuronium fentanyl
Reversal of muscle relaxation:	neostigmine/atropine/glycopyrrolate

The maximum total dose of fentanyl during the entire surgical procedure was 10 mg/kg.

For patients in the two ropivacaine groups, a continuous epidural infusion at a rate of 6 mL/hour of 2 mg/mL ropivacaine was initiated when wound pain at rest (defined as VAS = 10 mm) was present or, at the latest, two hours after surgery. Whenever the VAS at rest exceeded 30 mm, a 6 mL top-up dose (12 mg) was administered, followed by an increase of the infusion rate by 2 mL/hour. A minimum of 15 minutes between top-ups and infusion rate increases was required. The maximum allowed rate was 14 mL/hour (28 mg/hr) and the rate could be decreased and/or discontinued in case of excessive block. If patients experienced pain during physiotherapy, a 6 mL top-up dose was allowed and the infusion rate could be corrected.

For patients getting PCA morphine, it was started when would pain (defined as above) at rest was present, or within two hours of surgery. The PCA device delivered 1 mg boluses of morphine with a five minute lockout time.

Patients in the epidural infusion groups received that treatment for 24 hours post-surgery. They received analgesics as needed after that period. Patients in the PCA morphine groups received that treatment for 24 hours; or longer at the discretion of the investigator.

The primary measure of efficacy was the AUCM24 based on pain at rest measured by use of a VAS scale of 100 mm.

Secondary efficacy measures included:

1. AUCM for the intervals 0-4 hours and 0-8 hours;
2. VAS scores for wound pain at rest;
3. VAS scores equal to or greater than 30 mm;
4. VAS scores for wound pain after physiotherapy.

The following secondary efficacy measures appeared in the protocol but were not reported to have been measured in the final study report:

1. nausea, vomiting and pruritus events;
2. morphine consumption;
3. number of morphine requests;
4. spread of analgesia; and
5. degree of motor block.

Results:

A total of 106 patients were enrolled in the study, 33 randomized to the ropivacaine group, 37 to the ropivacaine plus PCA morphine group, and 35 to the PCA morphine alone group. One patient in the ropivacaine group and one patient in the PCA group received no study medication and were not included in any analyses. Five patients in the ropivacaine group and 3 in the ropivacaine plus PCA group were technical failures and were not included in the ITT (sponsor's APT group) group. Thirteen patients in the ropivacaine group, 14 in the ropivacaine plus PCA, and 15 in the PCA group were discontinued, for various reasons, and were not included in the PP analyses.

Treatment groups appeared to be generally matched on relevant measures at baseline.

Primary Efficacy Analyses:

The PCA morphine without ropivacaine group had a statistically significantly higher AUCM24 compared to the other two groups. No statistical significance was found between the ropivacaine alone and ropivacaine plus PCA morphine groups.[2]

AUCM24 Mean Values:

Ropivacaine	=	22
Ropivacaine + PCA	=	24
PCA	=	38

P-values for comparisons:

Ropivacaine vs. ropivacaine + PCA morphine	p=1.000
PCA morphine vs. Ropivacaine	p=0.003
PCA morphine vs. Ropivacaine + PCA morphine	p=0.001

[2] The p-values were adjusted using the Bonferroni multiple comparison method.

Secondary Efficacy Measures:

AUCM for the intervals 0-4 hours and 0-8 hours:

The sponsor reported statistically significantly higher AUCM values over each of these two intervals for the PCA morphine without ropivacaine group compared to the other two groups; and no statistically significant difference between the ropivacaine and the ropivacaine plus PCA morphine groups. However, they did not report the p-values.

Table 1. AUCM Values

AUCM	0-4 hours	0-8 hours
Ropivacaine	12	18
Ropivacaine + PCA	16	21
PCA	52	46

VAS scores for wound pain at rest:

The actual VAS scores were higher at most time points during the 24-hour period for the PCA morphine without ropivacaine group compared to the other two groups. Dr. Roberts has reproduced the sponsor's graphs summarizing these scores on page 110 of the medical review.

VAS scores equal to or greater than 30 mm:

The proportion of patients with VAS scores for pain at rest equal to or greater than 30 mm was consistently higher in the PCA morphine without ropivacaine group compared to the other two groups. Dr. Roberts has reproduced the sponsor's table summarizing these results on page 111 of the medical review.

VAS scores for wound pain after physiotherapy:

The VAS scores before and after physiotherapy tended to be lower for the ropivacaine and ropivacaine plus PCA groups compared to the PCA alone group. No statistical analysis was performed. Dr. Roberts' has reproduced the sponsor's table summarizing these results in her addendum to the medical review.

Comments:

While there does appear to be a consistent finding of improved pain control with epidural ropivacaine, with or without PCA morphine, compared to PCA morphine alone, the results of this study may be considered suspect due to the open-label design. The results of this study are what one would expect based on the known pharmacological behaviors of the study medications. This fact, in and of itself, provides significant room for the

introduction of bias in an open-label design.

Study SP-ROA-0010 (O14):

This was a multicenter, randomized, open-label, parallel group performed in France. Patients were randomized to one of the three treatment arms after major abdominal surgery:

1. Continuous epidural infusion of ropivacaine 2 mg/mL;
2. Continuous epidural infusion of ropivacaine 2 mg/mL and PCA morphine; or
3. PCA morphine.

Patients were premedicated with benzodiazepines administered at the discretion of the investigator. Patients also received prophylaxis for thrombosis and electrolyte solution infusion. All patients had general anesthesia for surgery and the following medications were allowed:

Induction and muscle relaxation:	thiopental atracurium/vecuronium/suxamethonium/pancuronium fentanyl
Maintenance:	isoflurane/nitrous oxide:oxygen atracurium/vecuronium/suxamethonium/ pancuronium fentanyl
Reversal of muscle relaxation:	neostigmine/atropine/glycopyrrolate

An epidural catheter was placed prior to surgery for patients who would be receiving ropivacaine. Within 30 minutes of the end of surgery, a 20 mL bolus of ropivacaine 2 mg/mL was administered via the catheter. Immediately following this, a continuous infusion of ropivacaine 2 mg/mL was initiated at a rate of 10 mL/hour. The infusion was not allowed to exceed 10 mL/hour during the 24 hour treatment period. In case of excessive block, the rate could be reduced to 6 mL/hour, or the infusion could be suspended until the block regressed to the desired level.

For patients who would be receiving PCA morphine, the device was connected when the patient was sufficiently awake after surgery. The PCA device was set to deliver 1.0 mg boluses of morphine with a lockout time of 5 minutes.

Rescue medication was available for all three groups and consisted of 1 to 2 mg boluses of intravenous morphine administered at the request of the patient and at the discretion of the investigator.

The primary measure of efficacy was the AUCM24 based on pain during coughing measured by use of a VAS scale of 100 mm.

Secondary efficacy measures included:

1. AUCM for the intervals 0-4 hours and 0-8 hours;
2. VAS scores for pain upon coughing;
3. VAS scores equal to or greater than 30 mm;
4. VAS scores for wound pain at rest;
5. AUCM for pain at rest;
6. VAS scores equal to or greater than 30 mm for pain at rest;
7. Spread of analgesia;
8. Motor block;
9. Total morphine consumption;
10. PCA morphine use;
11. Level of consciousness over time; and
12. Quality of pain relief.

Results:

A total of 141 patients were enrolled in the study. Of those 141, 43 were randomized to the ropivacaine group, 50 to the ropivacaine plus PCA morphine group, and 48 to the PCA morphine group. Three patients each were excluded from the safety population in the ropivacaine and ropivacaine plus PCA groups. One patient in the PCA alone group was excluded from the safety population. Two patients in the ropivacaine group and one patient each in the ropivacaine plus PCA group and the PCA alone group were excluded from the ITT population. Finally, one further patient in the ropivacaine plus PCA group was excluded from the PP population. Dr. Roberts' Table 68 in her addendum to the medical review summarizes the reasons for the discontinuations.

Treatment groups appeared to be generally matched on relevant measures at baseline.

Primary Efficacy Analyses:

The PCA morphine without ropivacaine group had a statistically significantly higher AUCM24 compared to the other two groups. No statistical significance was found between the ropivacaine alone and ropivacaine plus PCA morphine groups.[3]

Ropivacaine vs. ropivacaine + PCA morphine	p-value not provided
PCA morphine vs. Ropivacaine	p=0.024
PCA morphine vs. Ropivacaine + PCA morphine	p=0.003

[3] The p-values were adjusted using the Bonferroni multiple comparison method.

The mean AUCM24's for each group were:

Ropivacaine	36.21
Ropivacaine + PCA	30.62
PCA	48.82

Secondary Efficacy Measures:

AUCM for the intervals 0-4 hours and 0-8 hours:

For the 0-4 hour interval, the PCA morphine without ropivacaine group had a statistically significantly higher AUCM24 compared to the other two groups. No statistical significance was found between the ropivacaine alone and ropivacaine plus PCA morphine groups:

Ropivacaine vs. ropivacaine + PCA morphine	p-value not provided
PCA morphine vs. Ropivacaine	p=0.000
PCA morphine vs. Ropivacaine + PCA morphine	p=0.000

For the 0-8 hour interval, the PCA morphine without ropivacaine group had a statistically significantly higher AUCM24 compared to the other two groups. No statistical significance was found between the ropivacaine alone and ropivacaine plus PCA morphine groups:

Ropivacaine vs. ropivacaine + PCA morphine	p-value not provided
PCA morphine vs. Ropivacaine	p=0.000
PCA morphine vs. Ropivacaine + PCA morphine	p=0.000

Dr. Roberts has reproduced the sponsor's table summarizing the actual AUCM results on page 122 of the medical review.

VAS scores for pain upon coughing:

The actual VAS scores were higher at most time points during the 24-hour period for the PCA morphine without ropivacaine group compared to the other two groups, especially in the early post-operative period. Dr. Roberts has reproduced the sponsor's graphs summarizing these scores in her addendum to the medical review.

VAS scores equal to or above 30 mm:

The proportion of patients with VAS scores for pain upon coughing equal to or greater than 30 mm was consistently higher in the PCA morphine without ropivacaine group compared to the other two groups. These differences were statistically significant at some time points. However, an unbalanced number of patients were excluded from the

ropivacaine + PCA group vs. the PCA group at the 0-4 hour interval due to level of consciousness. Dr. Roberts has reproduced the sponsor's table summarizing these results on page 123 of the medical review.

VAS scores for wound pain at rest:

The actual VAS scores were higher at most time points during the 24-hour period for the PCA morphine without ropivacaine group compared to the other two groups, especially in the early post-operative period. Dr. Roberts has reproduced the sponsor's graphs summarizing these scores on page 124 of the medical review.

AUCM for pain at rest during the intervals: 0-4 hours, 0-8 hours and 0-24 hours:

There were statistically significantly higher AUCM values for the PCA morphine group compared to the other two groups at each interval. No statistically significant differences were found between the ropivacaine and the ropivacaine plus PCA morphine groups at any time interval. The p-values for the pairwise comparisons of the three treatments are summarized below:

Table 2.

	Ropivacaine vs. ropivacaine + PCA Morphine	**PCA Morphine vs. Ropivacaine**	**PCA Morphine vs. Ropivacaine + PCA Morphine**
0-4 hours	Not provided	0.000	0.000
0-8 hours	Not provided	0.000	0.000
0-24 hours	Not provided	0.016	0.002

Dr. Roberts has reproduced the sponsor's table summarizing the actual AUCM values on page 125 of the medical review.

VAS scores equal to or greater than 30 mm for pain at rest:

The proportion of patients with VAS scores for pain at rest equal to or greater than 30 mm was consistently higher in the PCA morphine without ropivacaine group compared to the other two groups. These differences were statistically significant at some time points. Dr. Roberts has reproduced the sponsor's table summarizing these results on page 125 of the medical review.

Spread of analgesia:

The spread of analgesia over time was similar in the two groups receiving ropivacaine. Dr. Roberts has reproduced the sponsor's graphs summarizing this data on page 126 of the medical review.

Motor block:
In general, patients who received ropivacaine plus PCA morphine had less motor block at all time points compared to patients who received ropivacaine alone.

Total morphine consumption:

The median total morphine consumption was 3.5 mg for the ropivacaine group, 19.0 mg for the ropivacaine plus PCA morphine group, and 51.2 mg for the PCA morphine alone group.

PCA morphine use:

The median number of PCA attempts was 21 for the ropivacaine plus PCA morphine group and 78 for the PCA morphine alone group. The median dose of PCA morphine per patient was 18.5 mg for the ropivacaine plus PCA morphine group and 41 mg for the PCA morphine alone group. Dr. Roberts has reproduced the sponsor's table summarizing PCA morphine use at different time intervals on page 129 of the medical review.

Level of consciousness over time:

The degree of sedation over time was similar in all three groups with the exception that in the PCA morphine alone group, less patients (4%) were awake and fully alert at 4 hours post-surgery than in the ropivacaine (18%) or the ropivacaine plus PCA morphine (18%) groups.

Quality of pain relief:

The following table summarizes the quality of pain relief assessments at various times post-surgery:

Table 3. % of Patients Rating Quality of Pain Relief as Good or Excellent

	Ropivacaine	Ropivacaine + PCA Morphine	PCA Morphine
22:00 day of surgery	**84**	**87**	**64**
08:00 day after surgery	**66**	**85**	**80**
End of treatment period	**79**	**85**	**83**

Comments:

While there does appear to be a consistent finding of improved pain control with epidural

ropivacaine, with or without PCA morphine, compared to PCA morphine alone, the results of this study may be considered suspect due to the open-label design. The results of this study are what one would expect based on the known pharmacological behaviors of the study medications. This fact, in and of itself, provides significant room for the introduction of bias in an open-label design.

Study SP-ROA-0010 (O15):

This was a randomized, open-label, parallel group study comparing epidural ropivacaine to general anesthesia followed by PCA morphine in patients recovering from total hip replacement. The study was performed at five centers in Germany.

Preoperative medications included benzodiazepines and prophylaxis for thrombosis. All patients received at least 500 mL of crystalloid. For patients randomized to the ropivacaine group, an epidural catheter was inserted preoperatively and , after a standard lidocaine test dose, 12 to 15 mL of ropivacaine 10 mg/mL (120-150 mg) was injected over 5 minutes. Surgery commenced when sensory block reached T10 and adequate surgical anesthesia had been achieved. If adequate block was not achieved by 30 minutes after the initial injection, an additional 5 to 10 mL was injected. If adequate block was not achieved within another 15 minutes, the patient received another aesthetic regimen at the discretion of the investigator. During surgery, additional 5 mL doses of ropivacaine could be injected as necessary. The maximum allowed total dose of ropivacaine was 250 mg.

For patients randomized to the PCA morphine group, general anesthesia was undertaken using combinations of the following allowed medications:

Induction and muscle relaxation:	thiopental/etomidate atracurium/vecuronium/succinylcholine/pancuronium fentanyl
Maintenance:	isoflurane/enflurane/nitrous oxide:oxygen/air:oxygen atracurium/vecuronium/succinylcholine/pancuronium fentanyl
Reversal of muscle relaxation:	neostigmine/atropine/glycopyrrolate

The total fentanyl dose was not allowed to exceed 3 µg/kg for induction or 2 µg/kg/hour for maintenance.

For the ropivacaine group, the epidural ropivacaine 2 mg/mL infusion commenced at 4-6 mL/hour (8-12 mg/hour) as soon as possible after the end of surgery, but not before the patient's Bromage score was < 2. The infusion was kept constant during the 24 hours. When the patient requested additional pain relief, 6 mL top-ups were administered at the discretion of the investigator, with a minimum of 30 minutes between top-ups. If excessive block occurred, the infusion was discontinued temporarily until the block regressed to the desired level. The infusion was discontinued at 24 hours after arrival at the post-anesthetic care unit (PACU). Additional 10 mL top-ups were allowed (with a 30 minute minimal interval between top-ups) over the next 24 hours and were administered as needed, at the discretion of the investigator. At 48 hours the catheter was removed.

For the PCA morphine group, 10 mg of intravenous morphine could be administered prior to the patient being connected to the PCA device. The PCA device was connected when the patient was fully awake. It delivered 1.0 mg intravenous boluses of morphine with a 5 minute lockout time. The dose could be increased to 1.5 mg at the discretion of the investigator. The PCA was disconnected at 48 hour after arrival at the PACU.

Additional postoperative medications for both groups included intravenous metamizole, or intravenous or intramuscular morphine.

The primary measure of efficacy was the AUCM24, area under the curve at 24 hours, based on VAS (Visual Analogue Scale of 100 mm) measurements for pain at rest.

Secondary efficacy measures included:

1. AUCM10 and AUCM48 based on VAS measurements for pain at rest;
2. Proportion of patients with VAS pain at rest scores equal to or greater than 30 mm at various time points;
3. VAS scores for pain at rest;
4. VAS scores for pain during mobilization;
5. Quality of pain relief;
6. Discomfort according to modified Gastrointestinal Symptom Rating Scale [see page 137 of the medical review for the definition of this scale.];
7. Time to readiness for discharge and actual discharge from PACU;
8. Time to readiness for discharge and actual discharge from hospital;
9. Consumption of metimazole;
10. Consumption of morphine in addition to PCA morphine;
11. Consumption of diclofenac.

Results:

Of the 90 patients enrolled in the study, 44 were randomized to the ropivacaine group and 46 to the PCA group. One patient from each group was excluded from the ITT population. The ropivacaine patient was discontinued due to technical failure and the PCA patient was rescheduled for a different operation. Three ropivacaine patients

(patient request due to severe pain, epidural catheter displacement and patient concern about sensory block) and one PCA patient (epidural catheter displacement) were excluded from the PP population.

Treatment groups appeared to be generally matched on relevant measures at baseline.

Primary Efficacy Analyses:

The mean AUCM24 for wound pain at rest was 14.3 ± 11.7 mm for the ropivacaine group and 24.0 ± 17.0 mm for the PCA group by analysis of the ITT group. This difference was statistically significant with p = 0.007.

Secondary Efficacy Measures:

AUCM10 and AUCM48 based on VAS measurements for pain at rest:

The mean AUCM's for pain at rest were lower for the ropivacaine group compared to the PCA morphine group at all centers at 10 and 48 hours after arrival in the PACU. These differences were statistically significant, p = 0.000.

Proportion of patients with VAS pain at rest scores equal to or greater than 30 mm at various time points:

The proportion of patients with VAS pain at rest scores equal to or greater than 30 mm was greater at all time points for the first 48 hours after surgery.

VAS scores for pain at rest:

The mean VS scores for pain at rest were generally lower in the ropivacaine group. However, the differences were small and the sponsor did not perform any statistical analyses on the data.

VAS scores for pain during mobilization:

Analyzing the proportion of patients with pain scores equal to or greater than 50 mm at various time points after arrival in the PACU, the patients in the ropivacaine group had lower scores until the afternoon of the second post-operative day after which the morphine treated patients had lower scores. The differences between the groups were rather small. No statistical analyses were performed. Dr. Roberts has summarized the results in Table 73, on page 148 of the medical review.

Quality of pain relief:

The proportion of patients reporting excellent or good pain relief was higher for the ropivacaine group for the first 3 to 7 hours after arrival at the PACU. Thereafter, through the night of the second day after arrival at the PACU, the proportion was higher for the morphine group. No statistical analyses were performed. Dr. Roberts has summarized the results in Table 73, on page 149 of the medical review.

Discomfort according to modified Gastrointestinal Symptom Rating Scale [GSRS]:

The sponsor reports that minor differences were seen between the treatment groups. No statistical analyses were performed. However, they do report that 72% of the ropivacaine group versus 42% of the morphine group still had a urinary catheter on the second postoperative day.

Time to readiness for discharge and actual discharge from PACU:

Mean time to readiness for discharge from PACU was consistently shorter for patients in the ropivacaine group at all centers. Differences between the groups for mean time to actual discharge were less distinct; and the actual discharge times were far longer than the times for "readiness." No statistical analyses were performed.

Time to readiness for discharge and actual discharge from hospital:

Mean time to readiness for discharge from hospital were slightly longer for the ropivacaine group at some centers, and slightly longer for the morphine groups at other centers. The times to actual discharge were similar in both groups as well. The sponsor reports that the median time to first flatus was shorter in the ropivacaine group (26 vs. 47 hours) and patients in the ropivacaine group were thought to be mentally clear and cooperative earlier than patients in the morphine group. Three patients in the morphine group had prolonged hospitalizations of greater than 35 days. No statistical analyses were performed.

Consumption of metamizole:

During the hospitalization, 51% of the ropivacaine treated patients and 42% of the morphine treated patients received mean doses of 2.69 ± 2.26 g and 1.64 ± 1.58 g, respectively. No statistical analyses were performed.

Consumption of morphine in addition to PCA morphine:

During the hospitalization, 9.3% of the ropivacaine treated patients and 66.7% of the PCA treated patients received morphine (in addition to the PCA morphine in that group).

The mean doses were 14.75 ± 7.32 mg and 8.47 ± 3.51 mg, respectively. No statistical analysis was performed.

Consumption of diclofenac:

From the third post-operative day onwards, diclofenac was administered to 65% of the ropivacaine treated patients versus 64% of the PCA morphine treated patients. The mean doses were 391 ± 288 mg and 371 ± 267 mg, respectively. No statistical analyses were performed.

Comments:

While there does appear to be a consistent finding of improved pain control with epidural ropivacaine compared to PCA morphine, the results of this study may be considered suspect due to the open-label design. The results of this study are what one would expect based on the known pharmacological behaviors of the study medications. This fact, in and of itself, provides significant room for the introduction of bias in an open-label design.

BRACHIAL PLEXUS BLOCK STUDIES:

Study SP-ROA-007 (P11):

This was a randomized, double-blind, parallel group, multicenter study comparing 30 mL of ropivacaine 7.5 mg/mL (225 mg) to 30 mL bupivacaine 5 mg/mL (150 mg) for subclavian perivascular brachial plexus block in patients undergoing surgery of the upper extremity. The study was performed at five centers in Canada.

Prior to the surgical procedure, a subclavian perivascular brachial plexus block was performed according to standard technique. Premedicants such as midazolam and fentanyl, and intraoperative medications such as propofol, midazolam and fentanyl were used at the investigator's discretion.

Sensory blockade was evaluated by pinprick with the following scale: 0 = no analgesia; 1 = analgesia; and 2 = anesthesia. Motor blockade was evaluated by nerve distribution specific maneuvers according to the following scale: 0 = no motor block; 1 = partial motor block; and 2 = complete motor block.

The primary measure of efficacy was the onset of analgesia in each of five nerves: axillary, radial, musculocutaneous, median, and ulnar.

Secondary efficacy measures included:

1. Onset of anesthesia, partial motor block, and complete motor block in each of the five nerves (measurements were performed at 10 minute intervals and, therefor, actual onset times were not observed, but were estimated by calculating the arithmetic mean of the assessment times before and after the block occurred);
2. Duration of each type of block in each of the five nerves (duration is defined as the time block disappears minus the time of onset with time of disappearance estimated by calculating the arithmetic mean of the assessment times before and after the block disappears);
3. Time until regression of analgesia for each nerve;
4. Time to first request for postoperative analgesics;
5. Quality of analgesia;
6. Quality of muscle relaxation;
7. Tourniquet pain;
8. Amount of concomitant sedative or analgesic medications administered during surgery.

Results:

Of the 106 patients enrolled in the study, 53 were randomized to the ropivacaine group and 51 to the bupivacaine group. The two patients were not randomized due broken study drug vials. One patient in the ropivacaine group did not receive study drug at the discretion of the investigator. Three patients in the ropivacaine group and one patient in the bupivacaine group were withdrawn from the efficacy analyses due to technical failures and one patient was withdrawn from the bupivacaine group due to an adverse event (generalized tonic-clonic seizure, probably due to intravascular injection). Thus, 49 patients in each group made up the ITT population. Data from seven patients was excluded from the per protocol (PP) analyses. Three patients were withdrawn from the ropivacaine group (one due to use of another anesthetic regimen and two due to insufficient duration of analgesia prior to surgery) and four patients were withdrawn from the bupivacaine group (one due to an inclusion criteria violation, one due to insufficient duration of analgesia prior to surgery, and two due to the use of another anesthetic regimen). Thus, 46 patients comprised the ropivacaine PP group and 45 patients comprised the bupivacaine PP group.

Three additional patients entered the study but were not included in any analyses due to the fact that they were not given proper informed consent. One of these patients received no study drug and the other two patients had mild adverse events, some of which may have been related to study drug. However, no further information was available from the sponsor. The sponsor reports that there are no data, graphics or other summary information regarding these patients.

Treatment groups appeared to be generally matched on relevant measures at baseline.

Primary Efficacy Analyses:

The onset times to development of analgesia in the ropivacaine and bupivacaine treated patients were not significantly different. Dr. Hartwell summarizes the results in her Table 6 on page 166 of the medical review. It is reproduced below:

Table 4. Analgesia Onset Time (minutes)

Nerve	*Analgesia*		
	Mean	SD	Median
Axillary			
Ropivacaine	13.2	11.0	7.0
Bupivacaine	15.4	12.5	15.0
Median			
Ropivacaine	12.3	12.6	5.0
Bupivacaine	11.6	8.3	6.5
Musculocutaneous			
Ropivacaine	10.8	10.2	5.0
Bupivacaine	12.9	10.2	7.0
Radial			
Ropivacaine	10.8	9.2	5.0
Bupivacaine	11.7	9.3	6.8
Ulnar			
Ropivacaine	9.1	6.8	5.0
Bupivacaine	12.6	10.7	6.5

[From sponsor's Table 1 "Summary Statistics", Item 8, Vol. 97, pp. 308-311]

Confidence intervals for the difference in the medians between the two treatments are summarized in Dr. Hartwell's Table 7 [page 166 of the medical review], reproduced below:

Table 5. 95% Confidence Intervals – Onset of Analgesia

Nerve	*Lower Bound*	*Upper Bound*	*Median Difference*
Axillary	-8.50	10.25	0.00
Median	-3.00	7.50	-2.50
M-cutaneous	-7.50	7.50	-2.50
Radial	-10.0	8.00	-2.00
Ulnar	-10.00	8.00	-2.00

[From sponsor's Table 12, Item 8, Vol. 96, p. 60]

No statistically significant differences were found. The log-rank p-values for all variables varied between 0.56 and 0.87.

Secondary Efficacy Measures:

Onset of anesthesia, partial motor block, and complete motor block in each of the five nerves:

There were no significant differences in the onset time to development of anesthesia, partial motor block, and complete motor block between the ropivacaine and bupivacaine groups for all nerves tested. Dr. Hartwell's Tables 8 and 9 [pages 167 and 168 of the medical review] summarize the onset times and confidence intervals for the difference in the medians between the treatment groups.

Duration of each type of block in each of the five nerves:

There were no significant differences in the duration of block (analgesia, anesthesia, partial motor, and complete motor) between the ropivacaine and bupivacaine groups for any of the tested nerves. Dr. Hartwell's Tables 9 and 10 [pages 168 and 169 of the medical review] summarize the duration times and confidence intervals for the difference in the medians between the treatment groups.

Time until regression of analgesia for each nerve:

The time to regression for each specific block was similar between the two study groups. As a summation of the two previous measurements, this data was not separately tabulated.

Time to first request for postoperative analgesics:

Forty-four ropivacaine treated patients and 41 bupivacaine treated patients requested postoperative analgesics. The median time to first request was 11.0 hours for the ropivacaine group and 12.2 hours for the bupivacaine group (confidence interval –4.62, 3.23).

Quality of analgesia and muscle relaxation:

Both the surgeons and the investigators evaluated the quality of analgesia and muscle relaxation at the end of the surgical procedure. No statistically significant difference was found between the study groups for either assessment. P-values were 0.2 and 0.8 for analgesia, and 0.5 and 0.7 for muscle relaxation.

Tourniquet pain:

Thirty-four patients in the ropivacaine group and 31 patients in the bupivacaine group were evaluated for tourniquet pain. Three patients in the ropivacaine group and 6 patients in the bupivacaine group experienced pain. The median onset of pain was 2.0 hours for the ropivacaine treated patients and 1.6 hours for the bupivacaine treated patients.

Amount of concomitant sedative or analgesic medications administered during surgery:

The use of sedative and analgesic medications was similar between the study groups. Dr. Hartwell's Table 16, page 174 of the medical review, summarizes those results.

Comments:

While no clinically or statistically significant differences were noted between the two treatment groups, the choice of comparing different dosages (30 mL of 7.5 mg/mL ropivacaine and 30 mL of 5 mg/mL bupivacaine) of the two study drugs is misleading. The only conclusion one may draw from this study is that 225 mg of ropivacaine 7.5 mg/mL and 150 mg of bupivacaine 5 mg/mL are not clinically or statistically significantly more or less effective than each other for subclavian perivascular brachial plexus block.

Study SP-ROA-0008 (P12):

This was a randomized, double-blind, parallel group, multicenter study comparing 40 mL of ropivacaine 7.5 mg/mL (300 mg) to 40 mL bupivacaine 5 mg/mL (200 mg) for axillary brachial plexus block in patients undergoing surgery of the upper extremity. The study was performed at five centers in Norway.

Prior to the surgical procedure, an axillary brachial plexus block was performed according to standard technique. Premedicants such as midazolam and diazepam, and intraoperative medications such as propofol, midazolam and fentanyl were used at the investigator's discretion.

Sensory blockade was evaluated by pinprick with the following scale: 0 = no analgesia; 1 = analgesia; and 2 = anesthesia. If adequate block of the surgical area was not achieved within 50 minutes, the investigator supplemented the block with a short acting local anesthetic such as lidocaine. The supplemented area was not included in the efficacy assessments. Motor blockade was evaluated by nerve distribution specific maneuvers according to the following scale: 0 = no motor block; 1 = partial motor block; and 2 = complete motor block.

The primary measure of efficacy was the onset of analgesia in each of five nerves: axillary, radial, musculocutaneous, median, and ulnar.

Secondary efficacy measures included:

1. Onset of anesthesia, partial motor block, and complete motor block in each of the five nerves (measurements were performed at 10 minute intervals and, therefor, actual onset times were not observed, but were estimated by calculating the arithmetic mean of the assessment times before and after the block occurred);
2. Duration of each type of block in each of the five nerves (duration is defined as the time block disappears minus the time of onset with time of disappearance estimated by calculating the arithmetic mean of the assessment times before and after the block disappears);
3. Time until regression of analgesia for each nerve;
4. Time to first request for postoperative analgesics;
5. Quality of analgesia;
6. Quality of muscle relaxation;
7. Tourniquet pain;
8. Amount of concomitant sedative or analgesic medications administered during surgery.

Results:

Of the 104 patients enrolled in the study, 53 were randomized to the ropivacaine group and 51 to the bupivacaine group. Two patients in the bupivacaine group were withdrawn from the efficacy analyses due to technical failures and one patient was withdrawn from the ropivacaine group due to an adverse event (seizure activity after intravascular injection). Thus, 49 patients in the bupivacaine group and 52 patients in the ropivacaine group made up the ITT population. Two patients in the ropivacaine group and one patient in the bupivacaine group did not meet inclusion criteria and their results were not analyzed as part of the PP analyses; one patient weighed more than 100 kg and two patients weighed less than 60kg. Thus, 50 patients comprised the ropivacaine PP group and 48 patients comprised the bupivacaine PP group.

Treatment groups appeared to be generally matched on relevant measures at baseline.

Primary Efficacy Analyses:

The onset times to development of analgesia in the ropivacaine and bupivacaine treated patients were not significantly different. Dr. Hartwell summarizes the results in her Table 6 on page 184 of the medical review. It is reproduced below:

Table 6. Analgesia Onset Time (minutes)

Nerve	*Mean*	*SD*	*Median*
Axillary			
Ropivacaine	19.9	12.2	20.0
Bupivacaine	19.6	12.7	20.0
Median			
Ropivacaine	12.7	13.0	5.0
Bupivacaine	10.3	8.6	5.0
Musculocutaneous			
Ropivacaine	16.1	12.7	15.0
Bupivacaine	13.9	11.2	7.5
Radial			
Ropivacaine	15.7	11.7	15.0
Bupivacaine	14.0	11.1	7.5
Ulnar			
Ropivacaine	13.2	9.7	7.5
Bupivacaine	12.2	10.9	5.0

[From sponsor's Table "Summary Statistics", Item 8, Vol. 100, p. 136]

Confidence intervals for the difference in the medians between the two treatments are summarized in Dr. Hartwell's Table 7 [page 184 of the medical review], reproduced below:

Table 7. 95% Confidence Intervals – Onset of Analgesia

Nerve	*Lower Bound*	*Upper Bound*	*Median Difference*	*Log-Rank p-value*
Axillary	NA	NA	-10.00	.1022
Median	0.00	2.50	0.00	.6649
M-cutaneous	-8.00	0.00	0.00	.1112
Radial	-8.00	2.00	0.00	.4122
Ulnar	-9.50	9.00	1.50	.0916

[From sponsor's Table 12, Item 8, Vol. 98, p. 81 and Item 8, Vol. 100, p. 158]

For the primary and secondary efficacy measures, the failure rate for the axillary and radial nerves (expected with technique of blockade) were no different for the ropivacaine and bupivacaine groups.

Secondary Efficacy Measures:

Onset of anesthesia, partial motor block, and complete motor block in each of the five nerves:

There were no significant differences in the onset time to development of anesthesia, partial motor block, and complete motor block between the ropivacaine and bupivacaine groups for all nerves tested. Dr. Hartwell's Tables 9 and 10 [pages 186 and 187 of the

medical review] summarize the onset times and confidence intervals for the difference in the medians between the treatment groups.

Duration of each type of block in each of the five nerves:

There were no significant differences in the duration of block (analgesia, anesthesia, partial motor, and complete motor) between the ropivacaine and bupivacaine groups for any of the tested nerves. Dr. Hartwell's Tables 12 and 13 [pages 189 and 190 of the medical review] summarize the duration times and confidence intervals for the difference in the medians between the treatment groups.

Time until regression of analgesia for each nerve:

The time to regression for each specific block was similar between the two study groups. As a summation of the two previous measurements, this data was not separately tabulated.

Time to first request for postoperative analgesics:

Forty-one ropivacaine treated patients and 35 bupivacaine treated patients requested postoperative analgesics. The median time to first request was 12.5 hours for the ropivacaine group and 13.5 hours for the bupivacaine group.

Quality of analgesia and muscle relaxation:

Both the surgeons and the investigators evaluated the quality of analgesia and muscle relaxation at the end of the surgical procedure. Statistically significant differences were found between the study groups for both assessments. Dr. Hartwell's Table 16, page 192 of the medical review, summarizes those results. P-values were 0.0002 and "not available" for analgesia, and 0.0004 and 0.0002 for muscle relaxation.

It should be noted, however, that this analysis included data from 34 patients who were considered to be "insignificant" protocol violators. Five of these patients, all in the bupivacaine group, had protocol violations that may have made a difference in the quality of block achieved. Four of those patients received less than the protocol specified 40 mL of bupivacaine and the other patient had an initial failed block and was subsequently administered a second block. Dr. Hartwell reanalyzed the data excluding those five patients. The results again demonstrated a statistically significant advantage for ropivacaine. Those results are summarized in Dr. Hartwell's Table 19, page 195 of the medical review.

Tourniquet pain:

Nine patients in the ropivacaine group and 12 patients in the bupivacaine group experienced pain. The median onset of pain was 2.3 hours for the ropivacaine treated patients and 1.8 hours for the bupivacaine treated patients.

Amount of concomitant sedative or analgesic medications administered during surgery:

The use of sedative and analgesic medications was similar between the study groups. Dr. Hartwell's Table 17, page 193 of the medical review, summarizes those results.

Comments:

While no clinically or statistically significant differences were noted between the two treatment groups (with the exception of the secondary endpoints quality of analgesia and muscle relaxation, which showed a statistically significant result favoring ropivacaine), the choice of comparing different dosages (40 mL of 7.5 mg/mL ropivacaine and 40 mL of 5 mg/mL bupivacaine) of the two study drugs is misleading. The only conclusion one may draw from this study is that 300 mg of ropivacaine 7.5 mg/mL and 200 mg of bupivacaine 5 mg/mL are not clinically or statistically significantly more or less effective than each other for axillary brachial plexus block; although this dose of ropivacaine may provide a better quality of anesthesia and better muscle relaxation than the dose of bupivacaine used in this study.

CESAREAN SECTION STUDIES:

Study 95RO89 (M09):

This was a randomized, double-blind, parallel group, multicenter study comparing 20-25 mL of ropivacaine 7.5 mg/mL to 20-30 mL bupivacaine 5 mg/mL epidural anesthesia in women scheduled for elective Cesarean section. The study was performed at two centers in Brazil and one center in South Africa.

Prior to the procedure, an epidural catheter was inserted. After a standard test dose of lidocaine, 20 mL of study drug was injected incrementally over 5 minutes. Surgery was initiated when a sensory block to T6 was confirmed and adequate surgical anesthesia had been achieved. Two additional 5 mL top-up doses were allowed at 10 minute intervals in order to achieve adequate anesthesia. Of note, the second top-up dose of for the ropivacaine group only consisted of 5 mL of saline without study drug. If adequate anesthesia had not been achieved at 40 minutes after administration of the initial dose, the patient received additional analgesics or anesthetics at the discretion of the investigator.

The primary measure of efficacy was pain at delivery measured on a numerical scale of 0 (no pain) to 100 (worst pain ever). For both primary and secondary efficacy analyses of

pain, patients who received additional anesthetic/analgesic treatment (above and beyond the protocol allowance) before the end of surgery were initially excluded and only the so-called "observed" values were analyzed. Those patients who received additional anesthetic/analgesic treatment were then assigned a score of "100" and added back into the database which was then reanalyzed.

Secondary efficacy measures included:

1. Pain at skin incision, closure of peritoneum, and last suture;
2. Quality of anesthesia based on analgesia and abdominal wall muscle relaxation;
3. Maximum upper spread of sensory block;
4. Time to onset of maximum sensory block;
5. Time to onset of T6 sensory level;
6. Time to complete regression of sensory block;
7. Maximum degree of motor block at 30 minutes post-surgery or later;
8. Time to complete regression of motor block.

Results:

A total of 126 patients were enrolled in the study. Of these 126 patients, 64 were randomized to the ropivacaine group and 62 to the bupivacaine group. Two patients in the ropivacaine group were withdrawn due to technical failure prior to receiving study drug. The ITT (APT or All Patients Treated, per sponsor) group consisted of 64 ropivacaine and 60 bupivacaine patients. Six patients in the ropivacaine group (4 due to technical failure and 2 due to receiving general anesthesia) and 3 patients in the bupivacaine group (1 due to an adverse event and 2 due to technical failure) were not included in the PP population.

There were 13 patients in each group who were discontinued early. The majority of these patients were discontinued due to lack of efficacy [see Dr. Hartwell's Table 1, page 2 of the her addendum to the medical review].

Treatment groups appeared to be generally matched on relevant measures at baseline.

Primary Efficacy Analyses:

The number of patients experiencing pain scores above zero during delivery was similar between the two groups (2 patients in the ropivacaine group and 4 patients in the bupivacaine group) for the "observed" scores. When patients who had received other anesthetic modalities were added into the analysis and assigned a score of 100, there was still no statistically significant difference between the groups. Dr. Hartwell's Table 7, page 210 of the medical review, summarizes the results and is reproduced below:

Table 8. Pain at Delivery

Treatment Group	With Observed Scores							With "100" Scores		
	N	# With NRS> 0	Median	Min	Max	p-value	Direction of Difference	N	p-value	Direction of Difference
Ropivacaine 7.5 mg/mL	52	2	0.0			.45494	I > II	60	.58065	I > II
Bupivacaine 5 mg/mL	55	4	0.0					58		

[From sponsor's Table 14, Item 8, Vol. 82, p. 68 and Item 8, Vol. 83, pp. 261-270]

Secondary Efficacy Measures:

Pain at skin incision, closure of peritoneum, and last suture:

There were no statistically significant differences between the two groups at any of these times. Dr. Hartwell's Table 8, page 211 of the medical review, summarizes the results.

Quality of anesthesia based on analgesia and abdominal wall muscle relaxation:

There were no statistically significant differences between the two groups for either of these outcome measures. Dr. Hartwell's Table 9, page 212 of the medical review, summarizes the results.

Maximum upper spread of sensory block:

The maximum upper spread of sensory block varied between T12 and C4 for the ropivacaine group and between T10 and T1 for the bupivacaine group. The differences between the groups was not statistically significant. Dr. Hartwell's Table 10, page 213 of the medical review, summarizes the results.

Time to onset of maximum sensory block:

There were no statistically significant differences between the two groups for time to onset of maximum sensory block. Dr. Hartwell's Table 11, page 214 of the medical review, summarizes the results.

Time to onset of T6 sensory level:

There were no statistically significant differences between the two groups for time to onset of T6 sensory level. Dr. Hartwell's Table 11, page 214 of the medical review, summarizes the results.

Time to complete regression of sensory block:

There were no statistically significant differences between the two groups for time to complete regression of sensory block. Dr. Hartwell's Table 11, page 214 of the medical review, summarizes the results.

Maximum degree of motor block at 30 minutes post-surgery or later:

There were no statistically significant differences between the two groups for maximum degree of motor block. Dr. Hartwell's Table 12, page 214 of the medical review, summarizes the results.

Time to complete regression of motor block:

There were no statistically significant differences between the two groups for time to complete regression of motor block. Dr. Hartwell's Table 13, page 215 of the medical review, summarizes the results.

Comments:

While no clinically or statistically significant differences were noted between the two treatment groups the choice of comparing different dosages (20-25 mL of 7.5 mg/mL ropivacaine and 20-30 mL of 5 mg/mL bupivacaine) of the two study drugs is misleading. The only conclusion one may draw from this study is that 150-187.5 mg of ropivacaine 7.5 mg/mL and 100-150 mg of bupivacaine 5 mg/mL are not clinically or statistically significantly more or less effective than each other as epidural anesthesia for Cesarean section.

Study 95RO91 (M10):

This was a randomized, double-blind, parallel group, multicenter study comparing 20-25 mL of ropivacaine 7.5 mg/mL to 20-30 mL bupivacaine 5 mg/mL epidural anesthesia in women scheduled for elective Cesarean section. The study was performed at eight centers in Canada.

Prior to the procedure, an epidural catheter was inserted. After a standard test dose of lidocaine, 20 mL of study drug was injected in increments of 4 mL every 2 minutes over 10 minutes. Surgery was initiated when a sensory block to T6 was confirmed and adequate surgical anesthesia had been achieved. Two additional 5 mL top-up doses were allowed at 10 minute intervals in order to achieve adequate anesthesia. Of note, the second top-up dose of for the ropivacaine group only consisted of 5 mL of saline without study drug. If adequate anesthesia had not been achieved at 40 minutes after administration of the initial dose, the patient received additional analgesics or anesthetics at the discretion of the investigator.

The primary measure of efficacy was pain at delivery measured on a numerical scale of 0 (no pain) to 100 (worst pain ever). For both primary and secondary efficacy analyses of pain, patients who received additional anesthetic/analgesic treatment (above and beyond the protocol allowance) before the end of surgery were initially excluded and only the so-called "observed" values were analyzed. Those patients who received additional anesthetic/analgesic treatment were then assigned a score of "100" and added back into the database which was then reanalyzed.

Secondary efficacy measures included:

1. Pain at skin incision, uterine exteriorization, closure of peritoneum/fascia, and last suture/clip;
2. Quality of anesthesia based on analgesia and abdominal wall muscle relaxation;
3. Maximum upper spread of sensory block;
4. Time to onset of maximum sensory block;
5. Time to onset of T6 sensory level;
6. Time to complete regression of sensory block;
7. Maximum degree of motor block at 30 minutes post-surgery or later;
8. Time to complete regression of motor block.

Results:

A total of 119 patients were enrolled in the study. Of these 119, 59 were randomized to the ropivacaine group and 60 to the bupivacaine group. Two patients in the ropivacaine group and 1 patient in the bupivacaine group did not receive study drug. The ITT (APT or All Patients Treated, per sponsor) group consisted of 57 ropivacaine and 59 bupivacaine patients. Four patients in the ropivacaine group and 12 patients in the bupivacaine group were found to have "lack of efficacy" and administered supplemental analgesics/anesthetics. These 16 patients were not included in the PP population.

There were 6 patients in the ropivacaine group and 13 patients in the bupivacaine group who discontinued early. The majority of these patients discontinued due to lack of efficacy [see Dr. Hartwell's Table 1, page 222 of the medical review].

Treatment groups appeared to be generally matched on relevant measures at baseline.

Primary Efficacy Analyses:

The number of patients experiencing pain scores above zero during delivery was similar between the two groups (13 patients in the ropivacaine group and 15 patients in the bupivacaine group) for the "observed" scores. When patients who had received other anesthetic modalities were added into the analysis and assigned a score of 100, there was still no statistically significant difference between the groups. Dr. Hartwell's Table 7, page 226 of the medical review, summarizes the results and is reproduced below: