

Table 9. 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	57	13	0.0			.45510	I < II	57	.26606	I < II
Bupivacaine 5 mg/mL	59	15	0.0					59		

[From sponsor's Table 16, Item 8, Vol. 86, p. 68 and Item 8, Vol. 87, pp. 261-271]

Secondary Efficacy Measures:

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

There were no statistically significant differences between the two groups in the amount of pain experienced at skin incision, uterine exteriorization, and peritoneal closure. There was a statistically significant ($p=0.008$) difference between the groups in the number of patients experiencing pain during the last suture. This difference favored the ropivacaine group. Dr. Hartwell's Table 8, page 227 of the medical review, summarizes the results.

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

There was a statistically significant difference between the two groups for the quality of analgesia ($p=0.037$). There was no statistically significant difference for the quality of muscle relaxation ($p=0.983$). Dr. Hartwell's Table 9, page 228 of the medical review, summarizes the results.

Maximum upper spread of sensory block:

The maximum upper spread of sensory block varied between T6 and C8 for the ropivacaine group and between T6 and C7 for the bupivacaine group. The differences between the groups was not statistically significant. Dr. Hartwell's Table 10, page 229 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:

The median time to regression of sensory block was 6.4 hours for the ropivacaine group and 5.5 hours for the bupivacaine group, with a p-value of 0.053. The minimum and maximum times were longer for the bupivacaine group. Dr. Hartwell's Table 11, page 230 of the medical review, summarizes the results.

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

The maximum degree of motor block was statistically significantly higher in the ropivacaine group (p=0.036). Dr. Hartwell's Table 12, page 230 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 231 of the medical review, summarizes the results.

Comments:

While no clinically or statistically significant differences were noted between the two treatment groups in the primary outcome measure, 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. While there were a few secondary outcome measures which indicated that this dose of ropivacaine may be more effective than the tested dose of bupivacaine in this setting, they also indicated that it may be significantly more potent for motor block. The only clearcut 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 95RO96 (M11):

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

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 15 and 10 minute intervals, respectively, 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. Administration of up to a total of 25 mL of ropivacaine 7.5 mg/mL (187.5 mg) or 30mL of bupivacaine 5 mg/mL (150 mg) was allowed. 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.

Following surgery, the patients were allowed to receive up to three top-up doses of study drug for pain management. These doses consisted of 8 mL of either ropivacaine 2 mg/mL or bupivacaine 2 mg/mL, i.e., 48 mg of either drug.

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

Results:

A total of 122 patients were enrolled in the study. Of these 122 patients, 83 were randomized to the ropivacaine group and 39 to the bupivacaine group. All 122 patients received study medication and were considered part of the ITT (sponsor's APT) group. Two patients in the ropivacaine group were considered technical failures and were not analyzed as part of the PP group.

There were 22 patients in the ropivacaine group and 12 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 239 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 (4 patients in the ropivacaine group and 0 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 8, page 242 of the medical review, summarizes the results and is reproduced below:

Table 10. 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	81	4	0.0			.15865	I > II	81	.08146	I > II
Bupivacaine 5 mg/mL	38	0	0.0					38		

[From sponsor's Table 13, Item 8, Vol. 90, p. 60 and Item 8, Vol. 91, pp. 189-198]

Secondary Efficacy Measures:

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

With analysis of observed scores, there were no statistically significant differences between the two groups in the amount of pain experienced at skin incision, uterine exteriorization, and last suture. There was a statistically significant ($p=0.003$) difference between the groups in favor of ropivacaine in the number of patients experiencing pain during peritoneal closure. With analysis incorporating the "100" scores, the only statistically significant ($p=.047$) difference between the treatment groups was for pain with uterine exteriorization. This difference was in favor of the bupivacaine group. One

patient had pain measurement only for skin incision because she received general anesthesia shortly after incision. Uterine exteriorization and peritoneal closure were not performed on all patients. Dr. Hartwell's Table 8, page 243 of the medical review, summarizes the results.

Discomfort at skin incision, delivery, uterine exteriorization, closure of peritoneum, and last suture:

There were no statistically significant differences between treatment groups in the amount of discomfort experienced at any of the timed measurements. Dr. Hartwell's Table 10, page 244 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 11, page 245 of the medical review, summarizes the results.

Maximum upper spread of sensory block:

The maximum upper spread of sensory block varied between T7 and T1 for the ropivacaine group and between T6 and C4 for the bupivacaine group. The differences between the groups was not statistically significant. Dr. Hartwell's Table 13, page 247 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 14, page 247 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 14, page 247 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 15, page 248 of the medical review, summarizes the results.

Comments:

While no consistent 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 96RO98 (M12):

This was a randomized, double-blind, parallel group, single center 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 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, uterine exteriorization, closure of peritoneum, and last suture;
2. Discomfort at skin incision, delivery, uterine exteriorization, closure of peritoneum, and last suture;
3. Quality of anesthesia based on analgesia and abdominal wall muscle relaxation;
4. Maximum upper spread of sensory block;
5. Time to onset of maximum sensory block;
6. Time to onset of T6 sensory level;
7. Maximum degree of motor block at 30 minutes post-surgery or later;

Results:

A total of 120 patients were enrolled in the study. Of these 120 patients, 60 were randomized to the ropivacaine group and 60 to the bupivacaine group. All 120 patients received study medication and were considered part of the ITT (sponsor's APT) group. Three patients in the ropivacaine group and 1 patient in the bupivacaine group were considered technical failures and were not analyzed as part of the PP group.

There were 5 patients in the ropivacaine group and 7 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 255 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 the same, 11, in the two groups 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 9, page 259 of the medical review, summarizes the results and is reproduced below:

Table 11. 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	56	11	0.0			.56785	I > II	57	.42612	I > II
Bupivacaine 5 mg/mL	59	11	0.0					59		

[From sponsor's Table 14, Item 8, Vol. 93, p. 58 and Item 8, Vol. 94, pp. 100-105]

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. Pain was not assessed for four patients in the ropivacaine group (3 technical failures, 1 given general anesthesia at skin incision) and for one patient in the bupivacaine group (technical failure). Pain on peritoneal closure and last suture was not assessed on one additional patient in the bupivacaine group who received additional analgesia. Uterine exteriorization and peritoneal closure were not performed in all cases. Dr. Hartwell's Table 10, page 260 of the medical review, summarizes the results.

Discomfort at skin incision, delivery, uterine exteriorization, closure of peritoneum, and last suture:

There were no statistically significant differences between treatment groups in the amount of discomfort experienced at any of the timed measurements. Discomfort was not assessed for four patients in the ropivacaine group (3 technical failures, 1 given general anesthesia at skin incision) and for one patient in the bupivacaine group (technical failure). Discomfort on peritoneal closure and last suture was not assessed on one additional patient in the bupivacaine group who received additional analgesia. Uterine exteriorization and peritoneal closure were not performed in all cases. Dr. Hartwell's Table 11, page 261 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 12, page 262 of the medical review, summarizes the results.

Maximum upper spread of sensory block:

The maximum upper spread of sensory block varied between T6 and C3 for the ropivacaine group and between T10 and C3 for the bupivacaine group. The differences between the groups was not statistically significant. Dr. Hartwell's Table 13, page 263 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 14, page 264 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 14, page 264 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 15, page 264 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.

STUDIES SUPPORTIVE OF EFFECTIVENESS:

Post-Operative Pain Studies:

Studies SP-ROA-0009 (O10) and SP-ROA-0010 (O11) compared the efficacy and safety of epidural ropivacaine alone versus in combination with fentanyl for the management of postoperative pain following colonic resection. Dr. Roberts' has thoroughly reviewed these two studies in the medical review (pages 46 – 99). However, as these trials were not comparing the product, which is the subject of this NDA, I will not review them in detail. As would be expected when a potent opioid analgesic such as fentanyl is added to the treatment regimen of epidural ropivacaine, the patients in the combination group experienced statistically significantly less pain than those treated with ropivacaine alone. In study O11, there were four treatment arms: ropivacaine alone and ropivacaine with increasing doses of fentanyl (1 μ g/mL, 2 μ g/mL, and 4 μ g/mL). The addition of increasing doses of fentanyl in this case, again as would be expected, resulted in a dosage effect which was statistically significant for the two higher doses compared to the ropivacaine alone.

Study 94RO83-01 (I32) was a pharmacokinetic study which comprised two, double-blind, parallel group, randomized groups treated postoperatively (total knee or hip replacement) with a continuous epidural infusion of either 20 mg/hour of 0.2% or 30 mg/hour of 0.3% ropivacaine. The efficacy measurements were amount of PCA required and VAS pain scores at rest. Five of the 24 patients who received an epidural infusion of ropivacaine for 72 hours did not require any PCA morphine; 2 in the 2 mg/mL group and 3 in the 3 mg/mL group. The median morphine consumption on days 1, 2, and 3 of treatment was 7, 6 and 2 mg for the 2 mg/mL group compared to 7, 9 and 2 mg in the 3 mg/mL group. The median number of PCA attempts on the three treatment days were 9, 7 and 3 in the 2 mg/mL group compared to 9, 13 and 3 in the 3 mg/mL group. The VAS scores at morning and evening over the three days were lower for the 3 mg/mL group and 0 for both groups by the morning of Day 3.

Study 94RO84 (09) was an uncontrolled pharmacokinetic study in 11 patients who received ropivacaine epidural block for major orthopedic surgery, followed by continuous epidural infusion of ropivacaine for postoperative pain management. VAS pain scores were low during the three day treatment period. Morphine use was also low.

Cesarean Section Studies:

Study 91RO47 (M04) was an open label study of the efficacy of 150 mg of ropivacaine 75% when used for epidural block for Cesarean section. Of the 38 patients enrolled, 26 had adequate block for surgery. The median onset of sensory block varied between 5 and 22.5 minutes and the median duration of block varied between 3.4 and 4.5 hours, depending on the dermatomal level. Quality of anesthesia judged by both the investigator and the patient was "satisfactory" in 25 of the 26 patients.

Study 94RO80 (M08) was an open label, non-randomized investigation of the efficacy, tolerability and pharmacokinetics of epidural administration of 150 mg, 187.5 mg and 225 mg of ropivacaine 7.5 mg/mL used for epidural block for Cesarean section. Eight women received the 150 mg dose and 8 women received the 187.5 mg dose. The high dose was dropped from the protocol. The incidence of pain, quality of surgical anesthesia and amount of muscle relaxation were comparable between the two groups. However, the upper dermatomal spread of the 187.5 mg dose was much higher than that of the 150 mg dose. Dr. Hartwell questions the ability of the results of this study to translate into clinical practice due to the method of drug injection (via a motorized syringe over a 5 minute period), which is significantly different from the intermittent injection technique more commonly undertaken.

Infiltration Nerve Block Studies:

Four studies of infiltration nerve block for postoperative pain management after inguinal herniorrhaphy were submitted with this supplement. However, the sponsor has not used the efficacy data from these studies to support an indication in the product labeling. As such, they have only been reviewed in brief by Dr. Roberts. I will not address these studies in this document, other than to acknowledge Dr. Roberts' impression that they were adequate and well-controlled and that all four showed a statistically significant effect for 40 mL ropivacaine 7.5 mg/mL (300 mg) compared to 40 mL bupivacaine 2.5 mg/mL (100 mg) or placebo. The patients treated in these studies are included in the safety data base.

SAFETY:

At the time that this supplement was submitted, a total of 264 patients had been exposed to 0.75% ropivacaine via epidural administration for Cesarean section; 119 patients had been exposed to 0.75% ropivacaine via brachial plexus block for upper extremity surgery; 445 patients had been exposed to 0.75% ropivacaine via epidural administration for management of postoperative pain; and, 282 patients had been exposed to 0.75% ropivacaine for either wound infiltration or field block after inguinal hernia repair. More complete exposure data, including information regarding rate and length of continuous infusion exposure in the postoperative pain management studies, is summarized in Dr. Roberts' Table 2, pages 18 and 19 of the medical review.

Deaths:

No patients died in the Cesarean section, brachial plexus or infiltration nerve block studies. Nine patients in the postoperative pain management studies died. All deaths occurred in Studies 010, 011 and 014. All of these patients received high levels of anesthesia, i.e. greater or equal to T5; 8/9 were exposed to 7.5 mg/mL ropivacaine; and, 7/9 were ASA III patients. While 8 of these deaths occurred in the two trials which compared the addition of fentanyl to epidural ropivacaine alone, the deaths do not appear to be related to fentanyl exposure; see Dr. Robert's breakdown, page 292 of the medical review.

The following are brief summaries of the patient deaths:

1. [Study O11] An elderly, ASA III male with multiple medical problems underwent a high anterior sigmoid colon resection for obstruction due to carcinoma. The total dose of ropivacaine was 112.5 mg given as 15 mL x 7.5 mg/mL plus 1047 mg as 2 mg/mL. The maximum rate of infusion was 14 mL/hour. He also received 2095 µg fentanyl. The highest level of block measured was C8. The patient developed acute pulmonary edema at 41 hours of treatment in the PACU and the infusion was discontinued. He then developed worsening cardiorespiratory function and multiorgan failure. He died 5 days postoperatively. The investigator attributed the death to recurarization due to renal failure. Dr. Roberts suggests that the death may have been due to the depressing effects of the high anesthetic level on the cardiac and respiratory systems.
2. [O11] An elderly, ASA III male with multiple medical problems underwent a gastrojejunostomy due to recurrent obstruction secondary to carcinoma of the colon. The total dose of ropivacaine was 60 mg given as 8 mL x 7.5 mg/mL plus 1655 mg as 2 mg/mL. The maximum rate of infusion was 14 mL/hour. No fentanyl was given. The highest level of block measured was T3. The patient's wound dehiscd eight days postoperatively and surgical repair was performed. The patient died six days later. The cause of death was attributed to oliguria and dyspnea secondary to colon cancer. Dr. Roberts agrees that this is the likely cause of death, but also speculates that post-infusion left ventricular failure requiring lasix, labored breathing and a high level of anesthesia may have resulted be an indication that the patient had experienced myocardial depression, which may have resulted in death.
3. [O11] A 51 year old, ASA III female with multiple medical problems underwent omentectomy, oophorectomy and salpingectomy due to metastatic ovarian carcinoma. Drainage of a subdiaphragmatic collection and oversewing of a liver laceration, as well as substantial blood loss complicated the surgery. The total dose of ropivacaine was 75 mg given as 10 mL x 7.5 mg/mL plus 1080 mg as 2 mg/mL. The maximum rate of infusion was 8 mL/hour. The highest level of block measured was T2. The postoperative course was complicated by multiple episodes of

hypotension requiring ephedrine. The infusion was discontinued on the third postoperative day. On the eighth postoperative day she developed bradycardia, tachypnea, diaphoresis and a depressed level of consciousness. She died later that day. E. Coli and anaerobes were cultured from her ascites and cause of death was attributed to sepsis due to feculent peritonitis. Dr. Roberts concurs but notes that the high level of anesthesia (never less than T5) may have contributed to the difficulty maintaining a constant infusion rate.

4. [O11] A 59 year old, ASA III female with multiple complications of ovarian cancer underwent a jejunocolic anastomosis and multiple gastroenterostomies. The total dose of ropivacaine was 60 mg given as 8 mL x 7.5 mg/mL plus 1952 mg as 2 mg/mL. The maximum rate of infusion was 14 mL/hour. The highest level of block measured was T2. Two weeks postoperatively she deteriorated due to disseminated cancer and treatment was withdrawn. She died four days later. Death was attributed to underlying metastatic carcinoma and Dr. Roberts concurs.
5. [O11] An elderly, otherwise healthy male underwent an anterior resection for carcinoma of the colon. The total dose of ropivacaine was 37.5 mg given as 5 mg x 7.5 mg/mL plus 714 mg as 2 mg/mL. The maximum rate of infusion was 14 mL/hour. He also received 357 µg fentanyl. The highest level of block measured was T2. Recurrent bradycardia and hypotension requiring atropine and aramine, respectively complicated the surgery. Twenty-four hours postoperatively, he was determined to have an inadequate block and the catheter was removed. He received an intercostal block with 75 mg of 7.5 mg/mL ropivacaine. One hour later he developed hypotension. He expired eight hours later. The death was attributed to myocardial infarction with cardiogenic shock. Dr. Roberts indicates that the myocardial infarction may have been drug induced.
6. [O10] A 51 year old, ASA III male with metastatic colon cancer underwent segmental transverse colon resection. The total dose of ropivacaine was 37.5 mg given as 5 mg x 7.5 mg/mL plus 1465.8 mg as 2 mg/mL. The maximum infusion rate was 10 mL/hour. The highest level of block measured was T3. He was discharged to home in stable condition. He died two months later. Dr. Roberts suggests that the patient most likely died secondary to advanced metastatic colon carcinoma.
7. [O10] A 64 year old, ASA III female with multiple medical problems underwent a low anterior resection of the sigmoid colon for carcinoma. The total dose of ropivacaine was 37.5 mg given as 5 mg of 7.5 mg/mL plus 195.4 mg as 2 mg/mL. She also received 195.4 µg fentanyl. The highest level of block measured was T2. Postoperatively the patient developed severe hypotension requiring fluid boluses and ephedrine, tachypnea, renal insufficiency and septic shock. A laparotomy was performed two days later for worsening sepsis and a large hole was found in the rectum, just below the anastomosis, with feculent peritonitis. A resection was performed, but postoperatively the patient continued to deteriorate and developed

multiorgan failure. Life support was withdrawn and she died. The death was attributed to sepsis with multiorgan failure secondary to the leaking surgical anastomosis. Dr. Roberts indicates that the combination of peripheral vascular disease (implying coronary vascular disease), advanced carcinoma and the high level and dose of anesthetic administered, with resultant vasodilation, may have resulted in decreased end organ perfusion and failure.

8. [O10] A 52 year old, ASA III male COPD and recurrent rectal cancer underwent an abdominal perineal rectal resection. The total dose of ropivacaine was 37.5 mg given as 5 mg of 7.5 mg/mL plus 1492.1 mg as 2 mg/mL. He also received 1417.1 µg fentanyl. The highest level of block measured was T5. The patient developed recurrent fever and was found to have liver and pelvic abscesses. He was treated with antibiotics and discharged after ten days. Four months later he was diagnosed with metastatic lesions and he died seven months later. The death was attributed to complications of metastatic rectal carcinoma. Dr. Roberts concurs with this assessment.
9. [O14] An elderly, ASA II male with multiple medical problems underwent bladder cystectomy for cancer. The total dose of ropivacaine was 506.3 mg given as 2 mg/mL. The surgery was complicated by 1800 mL blood loss. The highest level of block measured was T4. Postoperatively, the patient experienced multiple episodes of oxygen desaturation. The patient developed paresis of the leg adductors and was being treated with physiotherapy. Over a period of weeks the patient underwent multiple surgical procedures and experienced recurrent episodes of hyperthermia. However, the episodic hypoxia did not persist. His death was attributed to peritonitis due to perforation of the sigmoid colon and septic shock. Dr. Roberts concurs that this assessment, but notes that persistent hypoxemia may have impacted upon the patient's ability to heal postoperatively.

Dr. Roberts has concluded, based upon the information available regarding the above deaths, that the more concentrated formulation of ropivacaine used and the high levels of blockade are responsible for at least some of the patients' deaths. Based on the fact that local anesthetics are known to result in block of the cardiac acceleratory fibers and the nerve fibers responsible for diaphragmatic excursion, when given in high concentration and at high levels, she suggests that the complications reported in these patients are directly related to thoracic administration of the drug.

While this well known complication seen with high levels of block with the more concentrated formulations of local anesthetics would certainly suggest that similar problems are likely to occur with the 7.5 mg/mL ropivacaine formulation, I do not agree that the data available from the sponsor's studies confirm this hypothesis. None of the patients clearly died due to complications of exposure to a high block with ropivacaine 7.5 mg/mL. Indeed, Dr. Roberts only suggests the possibility in five out of the nine patients who did die. In addition, by comparing the patients who died in Studies O11 and

O10 with the patients in the two fentanyl studies who did not die, we were able to document the following:

1. Seven of the 8 patients who died were ASA III, where the majority of the patients who did not die were ASA I or II (325/406).
2. The maximum level of anesthesia was between T5 and C8 for the 8 patients who died and for 344 of the patients who did not die. Indeed, the maximum level of anesthesia was between C6 and C3 for 19 patients who did not die.
3. The mean dose of ropivacaine 7.5 mg/mL was slightly higher for the patients who died compared to the patients who did not die in Study O11 (84 mg vs. 66 mg) and was the same in both groups in Study O10 (37.5 mg).

Thus, although a small number of patients who received the 7.5 mg/mL ropivacaine and had high levels of block died, they were some of the most unstable patients in the studies. In addition, they did not receive a much greater amount of the concentrated ropivacaine than the patients who did not die; and most of the patients who did not die had higher or the same levels of anesthesia as those who did.

While the risk of morbidity and mortality due to high levels of concentrated local anesthetics is not in question, there is no evidence in this submission documenting an increased risk associate with ropivacaine compared to other drugs of this class.

Discontinuations:

Cesarean Section Studies:

No patients discontinued due to an adverse event in the Cesarean section studies. When study drug was ineffective, however, alternative anesthetic treatments were administered.

Brachial Plexus Block Studies:

In the brachial plexus studies, two patients had their treatment temporarily suspended due to adverse events. One experienced bradycardia to a 45 bpm, muscle twitching and temporary loss of consciousness after study drug injection, but recovered without intervention. The other patient experienced bradycardia, dizziness and hypotension, and required treatment with ephedrine and atropine; the actual numbers for these events are not available in either the tabulations or case report forms. Both patients reportedly completed the study and should not actually be considered discontinuations, but rather serious adverse events.

Infiltration Block Studies:

Although one patient with a possibly drug related cardiac adverse event (lateral ischemia by ECG, not confirmed by later evaluations) was considered discontinued from the study due to lack of post-treatment evaluations, he did receive the full dose of study medication.

There were no other discontinuations due to adverse events in the infiltration studies.

Postoperative Pain Studies:

In the postoperative pain studies O13, O14, and O15, the incidence of adverse events leading to discontinuation was highest for the ropivacaine only treated patients compared to the PCA morphine patients with or without ropivacaine. The most common adverse events leading to discontinuation in the ropivacaine only group were: hypotension (3%) and sciatica, bradycardia, ECG changes, postoperative pain, respiratory depression, and surgical complications (all 1.5%).

In the postoperative pain study O12, no patients who received ropivacaine were discontinued due to an adverse event, whereas one bupivacaine treated patient was discontinued due to an adverse event (confusion). In the postoperative pain studies O10 and O11, the incidence of discontinuations due to adverse events was similar in the ropivacaine alone and the ropivacaine plus fentanyl groups. Hypotension was the only adverse event resulting in discontinuation that occurred in greater than one percent of patients. It occurred in 1.4% of ropivacaine alone patients and 2% of ropivacaine plus fentanyl treated patients, resulting in permanent discontinuation from the study. It occurred in 11% of ropivacaine alone patients and 5% of ropivacaine plus fentanyl treated patients, resulting in temporary discontinuation of the study drug.

In the open label Study 09, a pharmacokinetic and clinical investigation of continuous epidural infusion of ropivacaine for postoperative pain management, 11/11 patients evaluable for safety developed fever. All fevers occurred after the ropivacaine infusion was started and the majority of the patients had recurrent febrile episodes despite treatment with acetaminophen. This study was discontinued due to the high incidence of fever. Patients in this study also had high incidences of other significant adverse events: hypotension (10/11), anemia (9/11), headache (8/11), bradycardia (6/11), chills (5/11), and urinary retention (5/11). A single investigator in Australia performed this study. All patients underwent major orthopedic surgery. The investigator attributed the episodes of fever to underlying infections in the majority of cases.

There has been suspicion in the past that exposure to high concentration ropivacaine (1%) by continuous epidural infusion may result in pyrexia [see medical review, page 326]. However, there were frequent incidences of febrile episodes in many of the other studies in this submission, most of which had patients exposed to lower concentrations than the 1% ropivacaine.

Serious Adverse Events:

Cesarean Section Studies:

In the Cesarean section studies the incidence of serious adverse events was approximately the same in the mothers; with hypotension the most frequent event occurring in 1.5% of the ropivacaine treated patients and 0% of the bupivacaine treated patients. There were one case each of ventricular arrhythmia and tachycardia. In the offspring, the overall incidence of serious adverse events was again similar, although there were differences in some individual events:

	<u>Ropi</u>	<u>Bupi</u>
Bradycardia, fetal	1.5%	0
Low Apgar	1.5%	0.5%
Asphyxia, neonatal	0.8%	0
Fever, neonatal	0.4%	1.8%
Jaundice, neonatal	0.8%	2.8%
Neonatal complications	0	1.8%

[based on sponsor's Table 6-7, Item 8, Volume 105, p.318]

Brachial Plexus Block Studies:

In the brachial plexus block studies, there were sixteen adverse events classified as serious. Of the events likely to have been due to study drug, there were two cases of convulsions, one in a bupivacaine treated patient and one in a ropivacaine treated patient. One case each of speech disorder and syncope occurred in ropivacaine treated patients. The two cases of convulsions, and possibly the episodes of speech disorder and syncope, were likely due to accidental intravascular injection.

Dr. Roberts' Table 87, page 313 of the medical review, identifies 8% ropivacaine treated and 2% bupivacaine treated patients with serious adverse events in the brachial plexus block studies likely to be drug related. She concludes that the higher incidence of serious toxicity in the ropivacaine group is due to the higher concentration. While this does seem to make sense based on our general understanding of the toxicity profile of local anesthetics, the numbers in this particular setting are too small to determine whether there is a statistically significant effect. In addition, the events documented here as CNS and cardiovascular toxicity are likely to be due, at least in some cases, to accidental intravascular injection, another factor in the equation which is based purely on technical skill and not the individual drugs' toxicity profiles.

Infiltration Block Studies:

The only ropivacaine treated patient with a serious adverse event was the patient noted above under discontinuations in Infiltration Block Studies.

Postoperative Pain Studies:

In the postoperative pain studies, Studies O13, O14 and O15 compared continuous epidural ropivacaine alone to PCA morphine alone and epidural ropivacaine with PCA morphine. Dr. Roberts' Table 91, page 322 of the medical review, summarizes the most common serious adverse events occurring in the three groups. It is reproduced below:

Table 12. Distribution of Unique Adverse Events – Ropivacaine versus PCA Morphine – Incidence >10%

PREFERRED TERM	ROPIVACAINE N=116 N(%)	ROPIVACAINE + PCA N=84 N(%)	PCA N=128 N(%)
Nausea	53(46)	40(48)	62(48)
Hypotension	56(48)	49(58)	51(40)
Fever	32(48)	33(39)	30(23)
Pain	35(30)	30(36)	26(20)
Anemia	30(26)	17(20)	26(20)
Hypoxia	17(15)	19(23)	28(22)
Hypertension	15(13)	15(18)	32(25)
Bradycardia	21(18)	8(10)	18(14)
Headache	18(16)	6(7)	5(4)
Urinary Tract Infection	8(7)	15(18)	6(5)
Postoperative Complications	19(16)	15(18)	22(17)
Pruritus	7(6)	11(13)	8(6)

[adapted from sponsor's table 11.1.3.1 see Appendix 5 for further details]

While hypotension and fever appeared to occur more frequently in the ropivacaine treated patients, hypertension and hypoxia appeared to occur more frequently in the morphine treated patients. Headache occurred far more frequently in the morphine alone treated patients, whereas urinary tract infection occurred most frequently in the ropivacaine plus morphine treated patients.

Review of the sponsor's Table 8-27, page 40, Volume 106, which displays all serious adverse events in each of the three groups, does not result in any other concerns. The events are generally similar in all three groups. There are no clinically unexpected events.

In Study O12, which compared continuous epidural infusion of ropivacaine versus bupivacaine, there appeared to be an increased number of possibly drug related serious adverse events in the bupivacaine treated patients. However, once again, a small number of patients and technical problems with administration complicate interpretation of these results. In the two small pharmacokinetic studies of epidural ropivacaine, the serious adverse event profiles are significant only for a case of elevated liver enzymes in one patient that resolved within 2 to 5 days and were not assessed to be drug related by the investigator.

In the two trials, which compared continuous epidural infusions of ropivacaine with and without fentanyl, the sponsor compared the incidence of serious adverse events occurring at greater than or equal to 70 hours versus less than 70 hours of continuous infusion. Prolonged continuous infusion did not appear to significantly increase the incidence of any serious adverse events. However, the addition of fentanyl to the patients' treatment regimen did increase the incidence of some serious adverse events, especially in the gastrointestinal, respiratory and urinary systems [see Dr. Roberts' Table 89, page 320 of the medical review].

Other Adverse Events:

Cesarean Section Studies:

The adverse event profile of 0.75% ropivacaine in these studies was as would be expected with a local anesthetic and was not significantly different than the profile of 0.5% bupivacaine. Review of the sponsor's Appendix Table 9-2, volume 106, page 99 through 103, reveals that the most frequent adverse events were hypotension (49% in the ropivacaine group; 52% in the bupivacaine group); nausea (25% in the ropivacaine group; 26% in the bupivacaine group); vomiting (9% in the ropivacaine group; 12% in the bupivacaine group); neonatal complications (15% in the ropivacaine group; 17% in the bupivacaine group); and neonatal jaundice (9% in the ropivacaine group; 11% in the bupivacaine group).

Brachial Plexus Block Studies:

The overall adverse event profiles of the ropivacaine and bupivacaine treated patients in these trials were similar; data from the comparative trials and all trials combined are similar. The most common adverse events were: nausea (22% of ropivacaine treated patients; 16% of bupivacaine treated patients); hypoesthesia (3% ropivacaine treated patients; 8% bupivacaine treated patients); pain (7% of each group); and vomiting (4% of ropivacaine treated patients and 7% of bupivacaine treated patients).

Infiltration Block Studies:

The adverse event profiles were similar in the ropivacaine and bupivacaine treated patients. The most frequently occurring events were: postoperative complications (5% in the ropivacaine group; 7% in the bupivacaine group) and nausea (6% in each group).

Postoperative Pain Studies:

In Studies O13, O14 and O15, the incidence of adverse events was similar with the three anesthetic regimens studied. Headache and back pain did occur with a significantly increased frequency in the ropivacaine alone treated patients [see Dr. Roberts' Table 98, page 332 of the medical review].

In Study O12, bradycardia occurred in 15% of the bupivacaine treated patients compared to 7% of the ropivacaine treated patients; however, the overall patient numbers are small.

In Studies O10 and O11, compared to patients who received continuous infusions of ropivacaine for less than 70 hours, in the patients who received continuous infusions for greater than or equal to 70 hours, the incidence of adverse events was twice as high in the nervous system, up to twice as high in the cardiovascular system, one and one half times as high in the gastrointestinal system, and twice as high in the urinary system. Dr. Roberts' Table 95, page 329 of the medical review, displays the adverse events occurring more frequently over time in descending order by body system. The addition of fentanyl to the treatment regimen did appear to increase the incidence of early postural hypotension, abnormal urine, late albuminuria, late urinary retention, and early atelectasis.

Laboratory Values:

Dr. Roberts reports that review of the clinical laboratory data found in the ISS, narrative summaries, case report forms and tabulations revealed no clinically significant and unexpected findings for any of the study groups. The finding of an increased incidence of isolated elevations in SGPT in the patients in the infiltration block studies is, as noted by Dr. Roberts, most likely spurious.

Vital Signs and ECG's:

Dr. Roberts reports that review of the vital sign and ECG data found in the ISS, narrative summaries, case report forms and tabulations revealed no clinically significant and unexpected findings for any of the study groups.

COMMENTS:

The sponsor has submitted an extensive body of data to support their proposed changes in the dosing regimen of ropivacaine as defined below:

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.”

Increased Dosing with Naropin 7.5 mg/mL:

In support of this change in dosing, the sponsor has submitted two studies for use in brachial plexus block, four studies for use during Cesarean section, and four studies for use in postoperative pain management.

Brachial Plexus Block:

No patients died in or discontinued from the brachial plexus block studies. While the incidence of serious adverse events was higher in the ropivacaine treated patients compared to the bupivacaine treated patients, the actual number of events was small for both groups and the most serious adverse events were likely to be the result of technical error, complicating interpretation. The overall adverse event profiles for the ropivacaine and bupivacaine treated patients were similar.

Cesarean Section:

While the four studies did document the effectiveness of the 7.5 mg/mL ropivacaine formulation, the results of all four studies showed no difference in efficacy for ropivacaine 7.5 mg/mL compared to bupivacaine 5 mg/mL. While a few secondary outcome measures in Study M10 indicated that ropivacaine was a more effective anesthetic in this setting, all of the primary endpoints, and the majority of secondary endpoints, did not show this difference. The finding of prolonged motor blockade with ropivacaine in Study M10 also bolsters the argument that any increased efficacy of ropivacaine is due to the higher dose used compared to bupivacaine, and, thus, the greater potency. No comparisons to bupivacaine regarding effectiveness are warranted based upon the data submitted.

A total of 264 patients were exposed to ropivacaine 7.5 mg/mL in the Cesarean section studies submitted in this supplement. No patients died or discontinued from the studies. The incidence of serious adverse events was similar in the ropivacaine and bupivacaine treated mothers. Although some differences in the frequency of serious adverse events were seen between the offspring groups, the events in question were expected complications with epidural block and they occurred in low numbers. The overall adverse event profile of ropivacaine 7.5 mg/mL was similar to bupivacaine 5 mg/mL.

Postoperative Pain Management:

This submission includes four controlled studies of postoperative pain management by continuous epidural infusion, some preceded by intraoperative epidural blockade.

However, none of the four studies uses the 7.5 mg/mL formulation. Thus, no conclusions may be directly drawn regarding its effectiveness or safety from those studies. However, two of the studies [O13 and O15] did include intraoperative epidural blocks with the 10 mg/mL formulation of ropivacaine. While efficacy cannot be established for the 7.5 mg/mL ropivacaine based on those two studies, some conclusions regarding safety are warranted. In addition, in the two studies that compared epidural ropivacaine with and without fentanyl [O10 and O11] intraoperative boluses of the 7.5 mg/mL formulation were administered. Therefore, a total of approximately 445 patients were exposed to the 7.5 mg/mL formulation.

Eight patients died in studies O10 and O11. However, none of those could be clearly attributed to study drug [see my discussion, page 44]. In the four controlled studies, the incidence of patients who discontinued was highest for the ropivacaine only treated patients compared to the patients treated with PCA morphine with or without ropivacaine. While it is difficult, based on the available analyses, to isolate the patients exposed to the 7.5 mg/mL ropivacaine formulation, the events responsible for discontinuation were those that would be expected with any epidural anesthetic block. In addition, those events did not occur with an unusually high frequency. Febrile episodes did occur in 11 out of 11 patients in one pharmacokinetic study (O9). However, febrile episodes also occurred frequently in patients exposed to lower concentrations in the other studies [see my discussion, page 46].

While there were some differences in the serious adverse event and overall adverse event profiles seen in the ropivacaine treated patients compared to the PCA morphine treated patients in the controlled trials, these differences were not of major clinical concern.

Increased Duration of Treatment to 72 Hours:

Only patients in Studies O10 and O11 were treated with epidural infusions of ropivacaine 7.5 mg/mL for 72 hours. As these studies were not controlled for the effectiveness of ropivacaine, no clear cut conclusions may be drawn regarding whether efficacy persists after 24 hours. However, the sponsor did compare the serious adverse event profiles and the overall adverse event profiles at less than 70 hours and greater or equal to 70 hours. Based on those analyses it appears that there was no evidence of loss of efficacy during the 24 to 70 hour period.

Prolonged continuous infusion of ropivacaine 7.5 mg/mL did not appear to increase the incidence of serious adverse events. However, the overall incidence of adverse events did appear to increase in patients treated for greater than or equal to 70 hours, particularly in the nervous, cardiovascular, gastrointestinal, and urinary systems.

Increased Epidural Infusion Rates:

For the major studies, only patients in Studies O13 (infusion rate up to 14 mL/hr; lumbar administration), O14 (infusion rate up to 10 mL/hr; lumbar or thoracic administration,

majority lumbar), and, O10 and O11 (infusion rates averaging 11 mL/hr; thoracic administration), met the criteria of increased rate compared to current labeling. However, these studies encompass exposure of over 400 patients to these increased rates. There was no evidence of decreased efficacy with these new rates. Nor did the safety findings in these studies raise any specific concerns.

RECOMMENDATIONS:

This supplemental application is approvable with appropriate labeling.

/s/

Bob A. Rappaport, M.D.

September 21, 1999
September 21, 1999

DOCUMENTATION OF TELECONFERENCE



Date: September 30, 1999

Between: FDA (HFD-170, Division of Anesthetics, Critical Care, and Addiction Drug Products).

SCSO: Corinne Moody

ISI

CSO: Susmita Samanta

And

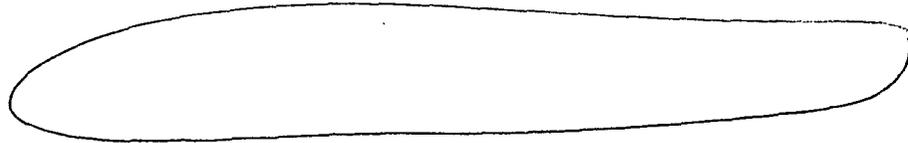
Company Name: AstraZeneca L.P.

Contact: Dr. Lisa Deluca

Phone: 610-695-1757

Topic: NDA 20-533/S-002, Naropin (ropivacaine HCl injection) Approvable letter, dated September 28, 1999

Discussion: FDA initiated the telecon to inform the sponsor of the following:



Drafted by S. Samanta 9/30/99

page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

DEC 14 1998

NDA 20-533/S-002

Astra Pharmaceuticals, L.P.
725 Chesterbrook Boulevard
Wayne, Pennsylvania 19087-5677

Attention: David J. Pizzi
Associate Director, Regulatory Affairs

Dear Mr. Pizzi:

Please refer to your pending September 24, 1998 New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Naropin (ropivacaine HCl monohydrate) Injection, 7.5 mg/mL.

We are reviewing the Pharmacokinetic section of your submission and have the following comments and information request.

1. Please summarize any studies available in the literature on PK information in the geriatric population and update the information in the package insert according to 21 CFR 201.57 (f)(10) in the NDA.
2. Please submit in the NDA, summarization of study(s) from the literature (along with articles) regarding the information of the effects of gender, race, age (e.g. pediatric use), renal and hepatic insufficiency on the pharmacokinetics of the drug. For those studies being currently conducted as a response to phase IV commitment, please provide the list of studies along with proposed timelines for completion.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Susmita Samanta, Project Manager, at (301) 827-7410.

Sincerely,

^ \ /S/

U
Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NOV 18 1998

Memorandum

Filing Meeting for NDA 20-533/S-002

Date: November 18, 1998

Sponsor: Astra Pharmaceuticals, L.P.

Drug: Naropin (ropivacaine HCl monohydrate)

Attendees:

Cynthia G. McCormick	Director
Bob Rappaport	Deputy Director
Monica Roberts	Medical Officer
Anwar Goheer	Reviewing Pharmacologist
Ramana Uppoor	Team Leader, Pharmacokinetics
Shinja Kim	Reviewing Pharmacokineticist
Tom Permutt	Reviewing Statistician
Corinne Moody	Chief Project Manager
Susmita Samanta	Project Manager

Discussion:

Background: The original application for NDA 20-533 was received by the agency on March 31, 1995.

The first action taken by the division was an approvable on June 28, 1998. The sponsor was asked to modify their label per our recommendations.

The sponsor was then granted an approval of their product on September 24, 1996, for the 2.0, 5.0, and 10.0 mg/mL.

Per our approval letter dated 9-24-96 the sponsor was encouraged to conduct additional trials in cesarean sections in order to gain approval of the 0.75% concentration of Naropin.

Each discipline was given the opportunity to give an overview of their threshold review of this efficacy supplement NDA 20-533/S-002. This supplement provides for increasing the dosage for nerve block anesthesia using Naropin from 5.0 mg/mL to 7.5 mg/mL and for extending the duration of treatment for postoperative analgesia using 2 mg/mL from 24 hours upto 72 hours.

Pharmacology:

- Review comments are attached

Pharmacokinetic:

- Review comments are attached

Statistics:

- Review comments are attached

Clinical:

- Review comments are attached

Recommendation:

Review team made a threshold determination that the application is sufficiently complete to permit a substantive review.

Action items:

- The review team decided to send the pk comments in an advice letter.



NDA 20-533/S-002

OCT 1 1998

Astra Pharmaceuticals, L.P.
725 Chesterbrook Boulevard
Wayne, PA 19087-5677

Attention: David J. Pizzi
Associate Director, Regulatory Affairs

Dear Mr. Pizzi:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Naropin™ (ropivacaine Hcl monohydrate) Injection Solution

NDA Number: 20-533

Supplement Number: 002

Date of Supplement: September 24, 1998

Date of Receipt: September 28, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on November 27, 1998 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and
Addiction Products, HFD-170
Office of Drug Evaluation III
Attention: Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

Sincerely

/s/
Connie Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III -
Center for Drug Evaluation and Research



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

MEDICAL OFFICER FWD PLANNING MEETING

NDA: 20-533

RELATED IND: 51-808

SPONSOR:

ASTRA Pharmaceuticals, LP

DRUG:

Naropin (Ropivacaine)

PROPOSED INDICATION:

**SURGICAL ANESTHESIA/ PAIN
CONTROL**

MEDICAL OFFICER:

MONICA L. ROBERTS, M.D.

151

DATE RECEIVED BY CDER:

September 28, 1998

REGULATORY ACTION:

Fileable

PROJECT MANAGER:

David Morgan

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SECTION 1.0 INTRODUCTION

SECTION 1.1 BACKGROUND

SECTION 1.1.1 Mechanism of Action of Local Anesthetics

Clinical local anesthesia is caused by blockade of the excitation-conduction process in nerves. The onset, depth, and duration of local anesthesia depends on the amount of the anesthetic dose that reaches the site of action and how rapidly it arrives and is removed from the receptor site. Eventually, local anesthetic molecules are distributed throughout all body tissues, but the relative concentration in different tissues varies as a function of vascular perfusion, tissue mass and time.

Local anesthetics have a direct effect on both cardiac muscle and vascular smooth muscle. These agents alter the heart's electrical and mechanical activity. Qualitative differences exist between the various local anesthetics. For example, bupivacaine may produce severe cardiac dysrhythmias, including ventricular fibrillation believed to be secondary to a direct cardiac effect.

SECTION 1.1.2 Drug History

SECTION 1.1.2.1 Marketed Drug History

Bupivacaine (Marcaine®, Abbott; Sensorcaine® Astra) is long-acting local anesthetic racemic mixture of the levo- and dextro- enantiomers [S(-)- and R(+)-, respectively], and is widely used both in the U.S. and abroad since the mid-1970's. It is currently approved for the "production of local or regional anesthesia for surgery, for oral surgery procedures, for diagnostic and therapeutic procedures, and for obstetric procedures. Only the 0.25% and 0.5% concentrations are indicated for obstetrical anesthesia", however. It is not recommended for intravenous regional anesthesia, pediatric populations under the age of 12 years or for post-operative pain management. (Physicians Desk Reference, 1998).

The rationale for development of ropivacaine, the l-isomer of bupivacaine, was based upon findings indicating that the l-isomer has equal potency to the d-isomer but is less cardiotoxic. In animal studies, ropivacaine was found to dissociate from the sodium channels more rapidly than bupivacaine, produce less accumulation of sodium channel blockade at physiologic heart rates, and is less cardiotoxic than bupivacaine. In humans, the potency and duration of action of ropivacaine are similar to those of bupivacaine but the risk of cardiotoxicity has not been completely eliminated.^{1,2,3}

¹ Redding JS, Pearson JW: Resuscitation from ventricular fibrillation (drug therapy), JAMA 203:255, 1968

Guildner CW: Resuscitation. Opening the airway: A comparative study of techniques for opening an airway obstructed / the tongue. JACEP 5:588, 1976

Barash PG, Clinical Anesthesia: Basic Principles of Pharmacology in Anesthesia Practice. Lippincott – Raven, 1997.

SECTION 1.1.2.2 Administrative History

In the USA, ropivacaine has been approved for surgical anesthesia and acute pain management in the following concentrations: 2.0, 5.0, 7.5, and 10 mg/ml. It was approved in 1996 and thus far has not encountered any problems relating to its safety or effectiveness – reportedly.⁴

SECTION 2.0 SUPPLEMENT to an APPROVED DRUG APPLICATION

Astra Pharmaceuticals, LP has submitted a series of clinical studies in support of a labeling change that would increase the dosage of ropivacaine used in peripheral nerve block (brachial plexus block), lumbar epidural for cesarean section, and thoracic epidural. Additionally, the submission requests an increase in the duration of epidural infusion for post-operative pain management.

This sNDA contains fourteen (14) clinical trials - 10 controlled and 4 uncontrolled - involving 1192 and 353 patients, respectively. Of the 1192 patients enrolled, 1150 (96.5%) were treated and 1110 (93.1%) patients were evaluated for efficacy. The open clinical trials demonstrated a similar completion profile with 330 (93.5%) patients treated and 330 (93.5%) being evaluated for efficacy, i.e. all patients treated were evaluable for efficacy.

⁴ Item 8, vol. 18.1, p. 36

SECTION 3.0 SCOPE AND DESIGN OF THE DEVELOPMENTAL PROGRAM

SECTION 3.1 CLINICAL STUDIES

SECTION 3.3.1 Description - Clinical Studies

There are fourteen (14) clinical trials - 10 controlled and 4 uncontrolled involving 1192 and 353 patients, respectively. The studies described as pivotal were conducted abroad, e.g., Brazil, Canada, Norway and South Africa.

The pivotal studies included the following:

1. Epidural Anesthesia for Cesarean Section – a total of 264 patients received 7.5 mg/ml of ropivacaine and 218 patients received 5 mg/ml bupivacaine
2. Major Nerve Block Anesthesia (Brachial Plexus Block) - a total of 105 patients received 7.5 mg/ml of ropivacaine and 102 patients received 5 mg/ml bupivacaine
3. Post – Operative Pain Management up to 72 hours - a total of 141 patients received 2 mg/ml of ropivacaine and 265 patients received ropivacaine (2 mg/ml) /fentanyl(1-4 ug/ml) mixture

The supportive clinical studies include the following:

US Conducted

1. Open Clinical Trial - Epidural Continuous Infusion for Post-Total Knee Replacement Pain – a total of 69 patients received ropivacaine and 35 patients received PCA morphine; 24 hour infusion

Non – US Conducted

1. Open Clinical Trial - Epidural Continuous Infusion for Post-Major Abdominal Surgery Pain – a total of 87 patients received ropivacaine and 47 patients received PCA morphine; 24 hour infusion
2. Open Clinical Trial - Epidural Continuous Infusion for Post-Total Hip Replacement Pain – a total of 44 patients received ropivacaine and 46 patients received PCA morphine; 48 hour infusion
3. Double-Blind - Epidural Continuous Infusion for Post-Total Knee Replacement Pain – a total of 27 patients received ropivacaine and 27 patients received bupivacaine; 24 hour infusion
4. Open Clinical Trial - Epidural Anesthesia for Cesarean Section – a total of 32 patients received 7.5 mg/ml ropivacaine

SECTION 3.3.2 Outline - Clinical Studies

SECTION 3.3.2.1 Study # 132 94R083

- ❖ double - blind, randomized, parallel
- ❖ 72 hour continuous epidural infusion
- ❖ 2 mg/ml or 3 mg/ml ropivacaine (20 or 30 mg/h)
- ❖ N = 24 (12 per treatment group)
- ❖ Major Orthopedic Surgery (knee or hip surgery)
- ❖ age 18 - 80;
- ❖ males and females
- ❖ Primary Objective – to estimate the plasma concentration –time profile of ropivacaine based on both total and free concentrations when infused epidurally for 72h and to compare the pharmacokinetic variables obtained for two groups, using two different infusion rates
- ❖ Results
 - ❖ Efficacy - Post-op pain was, "... generally well controlled"⁵
 - ❖ Safety - Transient Increased liver enzymes 11 days post – infusion,
- Five most common AE – hypotension, n/v, bradycardia, hypertension, fever

SECTION 3.3.2.2 Study # O12 94Ro85

- ❖ double - blind, randomized, parallel
- ❖ 24 hour continuous epidural infusion
- ❖ 2 mg/ml ropivacaine (8 ml/h) or 2 mg/ml bupivacaine
 - ❖ Rescue medication – PCA morphine
- ❖ N = 54 (27 per treatment group)
- ❖ Total Knee Replacement
- ❖ age 18-75
- ❖ males and females
- ❖ Primary Objective – to compare ropivacaine and bupivacaine administered post-operatively after total knee replacement, with regard to both pain at rest and motor block.
- ❖ Results
 - ❖ Efficacy – "... 16 mg/h of epidural infusion of ropivacaine or bupivacaine combined with PCA morphine appears to provide effective and well-tolerated analgesia for 24 hours following total knee replacement. While **pain scores are slightly greater for ropivacaine, the degree of motor block is consistently lower throughout treatment.**"
 - ❖ Safety - Most common AE – hypotension, n/v, fever

SECTION 3.3.2.3

Study # O10 Sp-ROA-0009

- ❖ double - blind, randomized, parallel
- ❖ 24 hour continuous epidural infusion
- ❖ Epidural block established with 7.5 mg/ml prior to surgery followed by a continuous infusion of 2 mg/ml ropivacaine (8 ml/h) +/- 2 ug/ml fentanyl
 - ❖ Infusion adjusted during the 72 h period – 4 –14 ml/h
- ❖ N =162
- ❖ Colonic Resection
- ❖ age 18-75
- ❖ males and females
- ❖ Primary Objective – to compare each patient's mean infusion rate in patients receiving continuous epidural infusion of ropivacaine 2 mg/ml alone and ropivacaine 2 mg/ml + fentanyl 2 ug/ml administered for postoperative pain management following colonic resection. All patients received ketorolac
- ❖ Results
 - ❖ Efficacy – Epidural infusion of 4-14 ml/h of ropivacaine, "... provides effective analgesia for up to 73 hours following colonic resection, with ketorolac as sole adjunct analgesia. The admixture of fentanyl 2 ug/ml resulted in more effective pain relief, a decrease in the epidural infusion rate without reduction of motor block, but an increase in the incidence of hypotension and longer hospital stay."
 - ❖ Safety - Most common AE – hypotension, n/v, fever, oliguria
 - Ropivacaine + Fentanyl: 1 **cardiac failure**, 1 hypokalemia, 1 **renal failure**, 3 hypotension; 90 SAE compared to 27 for the ropivacaine alone group

SECTION 3.3.2.4

Study # O11 Sp-ROA-0010

- ❖ double - blind, randomized, parallel
- ❖ 72 hour continuous epidural infusion
- ❖ Epidural block established with 7.5 mg/ml prior to surgery followed by a continuous infusion of 2 mg/ml ropivacaine (8 ml/h) +/- 1, 2, or 4 ug/ml fentanyl
 - ❖ Infusion adjusted during the 72 h period – 4 –14 ml/h
- ❖ N =268
- ❖ Major Abdominal Surgery
- ❖ age 18-79
- ❖ males and females
- ❖ Primary Objective – to compare each patient's mean infusion rate in patients receiving continuous epidural infusion of ropivacaine 2 mg/ml alone, and ropivacaine 2 mg/ml + 1 ug/ml fentanyl, ropivacaine 2 mg/ml + 2 ug/ml fentanyl ropivacaine, and ropivacaine 2 mg/ml + 4 ug/ml fentanyl administered for postoperative pain management following major abdominal surgery. All patients received additional paracetamol (acetaminophen).
- ❖ Results
 - ❖ Efficacy – Epidural infusion of 4-14 ml/h of ropivacaine, "... provides effective analgesia for up to 73 hours following colonic resection, with ketorolac as sole adjuvant analgesia. The admixture of fentanyl 2 ug/ml resulted in more effective pain relief, a decrease in the epidural infusion rate without reduction of motor block, but an increase in the incidence of hypotension and longer hospital stay."
 - ❖ Safety - Most common AE – hypotension, n/v, fever, oliguria, dizziness, pruritus, oliguria
 - Ropivacaine + 4 ug/ml Fentanyl: 1 respiratory failure, Twice as many SAE compared to other three groups

SECTION 3.3.2.5

Study # M09 95RO89

- ❖ double - blind, randomized, parallel
- ❖ 7.5 mg/ml Ropivacaine vs. 5.0 mg/ml Bupivacaine
- ❖ N =126
- ❖ Cesarean Section
- ❖ age >18
- ❖ females with full-term single fetus
- ❖ Primary Objective – to evaluate the efficacy and tolerability of ropivacaine 7.5 mg/ml and bupivacaine 5 mg/ml used for cesarean section. Evaluation was understood as the estimation of treatment differences with respect to efficacy and tolerability variables. The primary efficacy variable was pain on delivery. The primary tolerability variable was maximum drop in maternal blood pressure.
- ❖ Results
 - ❖ Efficacy – “Epidural ropivacaine 7.5 mg/ml in doses up to 187.5 mg produces surgical anesthesia which is equally effective as that of bupivacaine 5 mg/ml, 150 mg.”
 - Safety
 - “The clinical safety of ropivacaine has been found to be as good as that for bupivacaine in these doses.”
 - Most frequent AE’s were maternal hypotension and uterine hypotonia, and fetal bradycardia, low APGARs and NOS

SECTION 3.3.2.6

Study # M10 95RO91

- ❖ double - blind, randomized, parallel
- ❖ 7.5 mg/ml Ropivacaine vs. 5.0 mg/ml Bupivacaine
- ❖ N =119
- ❖ Cesarean Section
- ❖ age >18
- ❖ females with full-term single fetus
- ❖ Primary Objective – to evaluate the efficacy and tolerability of ropivacaine 7.5 mg/ml and bupivacaine 5 mg/ml used for cesarean section. Evaluation was understood as the estimation of treatment differences with respect to efficacy and tolerability variables. The primary efficacy variable was pain on delivery. The primary tolerability variable was maximum drop in maternal blood pressure.
- ❖ Results
 - ❖ Efficacy – “...epidural ropivacaine 7.5 mg/ml in doses up to 187.5 mg produces surgical anesthesia which is more effective, in terms of quality of anesthesia and pain during surgery, compared to bupivacaine 5 mg/ml, 150 mg.”
 - Safety
 - “The clinical safety of ropivacaine has been found to be at least as good as that of bupivacaine in these doses.”

SECTION 3.3.2.7

Study # M11 96RO96

- ❖ double - blind, randomized, parallel
- ❖ 7.5 mg/ml Ropivacaine vs. 5.0 mg/ml Bupivacaine
- ❖ N =122
- ❖ Cesarean Section
- ❖ age >18
- ❖ females with full-term single fetus
- ❖ Primary Objective – to evaluate the efficacy and tolerability of ropivacaine 7.5 mg/ml and bupivacaine 5 mg/ml used for cesarean section. Evaluation was understood as the estimation of treatment differences with respect to efficacy and tolerability variables. The primary efficacy variable was pain on delivery. The primary tolerability variable was maximum drop in maternal blood pressure.
- ❖ Results
 - ❖ Efficacy – "...epidural ropivacaine 7.5 mg/ml in doses up to 187.5 mg produces surgical anesthesia which is equally effective, in terms of quality of anesthesia and pain during surgery, compared to bupivacaine 5 mg/ml, 150 mg."
 - Safety - "A statistically significant more profound drop in systolic blood pressure was evident in the patients in the ropivacaine group" Most frequent AE: maternal hypotension, nausea and fetal congenital anomaly/jaundice
[Note; discuss with colleague]

SECTION 3.3.2.8

Study # M12 96RO98

- ❖ double - blind, randomized, parallel
- ❖ 7.5 mg/ml Ropivacaine vs. 5.0 mg/ml Bupivacaine
- ❖ N =120
- ❖ Cesarean Section
- ❖ age >18
- ❖ females with full-term single fetus
- ❖ Primary Objective – to evaluate the efficacy and tolerability of ropivacaine 7.5 mg/ml and bupivacaine 5 mg/ml used for cesarean section. Evaluation was understood as the estimation of treatment differences with respect to efficacy and tolerability variables. The primary efficacy variable was pain on delivery. The primary tolerability variable was maximum drop in maternal blood pressure.
- ❖ Results
 - ❖ Efficacy – "...epidural ropivacaine 7.5 mg/ml in doses up to 187.5 mg produces surgical anesthesia which is equally effective, in terms of quality of anesthesia and pain during surgery, compared to bupivacaine 5 mg/ml, 150 mg."
 - ❖ Safety - "at least as safe as" Most frequent AE: maternal hypotension, headache and nausea and fetal NOS

SECTION 3.3.2.9

Study # P11 Sp-ROA-0007

- ❖ double - blind, randomized, parallel
- ❖ 7.5 mg/ml Ropivacaine (225 mg) vs. 5mg/ml Bupivacaine (150mg)
- ❖ N =106
- ❖ Brachial Plexus Block
- ❖ age 18 - 75
- ❖ males and females
- ❖ Primary Objective – to investigate the efficacy of ropivacaine 7.5 mg/ml compared with bupivacaine 5 mg/ml when used for subclavian perivascular brachial plexus block. The primary measure of efficacy was the onset of analgesia.
- ❖ Results
 - ❖ Efficacy – “There was so statistically significant difference between treatments in the onset and duration of sensory and motor block in any of the five nerves, nor the quality of anesthesia”
 - ❖ Safety - “There was no clinically significant differences in systolic and diastolic blood pressure and pulse rate.
 - ❖ Most frequent AE: nausea. Two serious AE were reported in the ropivacaine group – unlikely causal relationship

SECTION 3.3.2.10

Study # P12 Sp-ROA-0008

- ❖ double - blind, randomized, parallel
- ❖ 7.5 mg/ml Ropivacaine (300 mg) vs. 5mg/ml Bupivacaine (200 mg)
- ❖ N =104
- ❖ Brachial Plexus Block
- ❖ age 19 - 75
- ❖ males and females
- ❖ Primary Objective – to investigate the efficacy of ropivacaine 7.5 mg/ml compared with bupivacaine 5 mg/ml when used for axillary brachial plexus block. The primary measure of efficacy was the onset of analgesia.
- ❖ Results
 - ❖ Efficacy – ...produced safe and effective surgical anesthesia of sufficient duration. The onset of analgesia was similar in both groups, but the quality of anesthesia and motor block was... superior to that produced by bupivacaine
 - ❖ Safety - “There was so clinically significant differences in systolic and diastolic blood pressure and pulse rate.
Most frequent AE: nausea, bradycardia and dizziness.

- ❖ Open, randomized, parallel
- ❖ 72 hour continuous epidural infusion
- ❖ Three Treatment Groups
 - ❖ 10 mg/ml ropivacaine (100 – 250 mg) followed by 2 mg/ml ropivacaine (6-14 ml/h) for 24 hours;
 - ❖ 10 mg/ml ropivacaine (100 – 250 mg) followed by 2 mg/ml ropivacaine (6-14 ml/h) for 24 hours – combined with PCA morphine (1 mg bolus with five-minute lock – out time)
 - ❖ GA followed by PCA morphine (1 mg bolus with five-minute lock – out time)
- ❖ N = 106
- ❖ Total Knee Replacement
- ❖ age 20 - 86;
- ❖ males and females
- ❖ Primary Objective – to compare the efficacy and tolerability of the three treatments. The primary measure of efficacy was pain at rest. Tolerability was evaluated by recording subjective symptoms and adverse events
- ❖ Results
 - ❖ Efficacy – “Epidural anesthesia with ropivacaine 10 mg/ml followed by a continuous infusion of 2 mg/ml offers effective and well-tolerated anesthesia for total knee replacement and superior post – op pain relief at rest compared to PCA morphine . The addition of PCA morphine did not offer any advantages
 - ❖ Safety - The most frequently reported adverse event during the 24 hour infusion period was hypotension – before surgery it was highest in the PCA group, during surgery and the following 24 hours – highest in the two groups receiving ropivacaine. The other most frequently reported adverse events were nausea, pain, fever and constipation

SECTION 3.3.2.12

Study # O14 94R082

- ❖ Open, randomized, parallel
- ❖ 24 hour infusion
- ❖ Three Treatment Groups
 - ❖ 2 mg/ml ropivacaine infusion
 - ❖ 2 mg/ml ropivacaine infusion combined with PCA morphine
 - ❖ PCA morphine
- ❖ Rescue medication – morphine 1 –2 mg, iv
- ❖ N =141
- ❖ Major Abdominal Surgery
- ❖ age 26-75
- ❖ males and females
- ❖ Primary Objective – to compare continuous infusion of 2 mg/ml ropivacaine, 2 mg/ml ropivacaine + PCA morphine and PCA morphine alone with regard to coughing. The tolerability was studied by recording subjective symptoms and adverse events.
- ❖ Results
 - ❖ Efficacy – “Epidural ropivacaine (2 mg/ml with or without PCA morphine) is found to give superior postoperative pain relief both at rest and upon coughing...when compared to PCA morphine alone”
 - ❖ Safety - Most common AE – hypotension, hypertension, n/v, fever, hypoxia

SECTION 3.3.2.13

Study # O15 95RO93

- ❖ open, randomized, parallel
- ❖ 24 hour continuous epidural infusion
- ❖ Treatment Groups
 - ❖ Surgery: 10 mg/ml Ropivacaine; Postop: 2 mg/ml ropivacaine infusion + top-ups 0-48 h
 - ❖ Surgery: general anesthesia Postop: PCA morphine
- ❖ Total Hip Replacement
- ❖ age 49-75
- ❖ N = 90
- ❖ males and females
- ❖ Primary Objective – to compare the efficacy and tolerability of the two anesthetic approaches and postoperative pain management following the continuous infusion of 2 mg/ml ropivacaine, 2 mg/ml ropivacaine + PCA morphine and PCA morphine alone with regard to coughing. The tolerability was studied by recording subjective symptoms and adverse events.
- ❖ Results
 - ❖ Efficacy – “Epidural anesthesia followed by epidural ropivacaine for pain control is more effective in the controlling post-op pain than general anesthesia followed by PCA morphine to PCA morphine alone”
 - Safety Equally safe. Most common AE – hypotension, hypertension, n/v, fever, hypoxia

SECTION 3.3.2.14

Study # M12 96RO98

- ❖ open, randomized, parallel
- ❖ 7.5 mg/ml Ropivacaine vs. 5.0 mg/ml Bupivacaine
- ❖ N = 16
- ❖ Cesarean Section
- ❖ age >18
- ❖ females with full-term single fetus
- ❖ Primary Objective – to evaluate the efficacy, tolerability and pharmacokinetics of epidural administration of ropivacaine 7.5 mg/ml (150 mg, 187.5 mg, and 225 mg) when used for cesarean section
- ❖ Results
 - ❖ Efficacy – “The doses 150 mg and 187.5 mg ropivacaine gave excellent anesthesia. The treatments were well tolerated by mothers and fetuses in both groups. The maximum maternal free venous plasma concentrations, ... were well below the threshold ... levels for CNS symptoms. However, excessive upper sensory blocks... and hypotension was larger in the 187.5 mg group. Therefore 150 mg was selected for the main dose in comparative studies, with an option to give an extra 37.5 mg in case of inadequate surgical anesthesia.
 - ❖ Safety - No serious adverse event were reported. No adverse event were reported for fetuses or newborns. The most common maternal adverse event was hypotension

C. Foreign Marketing History

1. Overview

Naropin® Injection (ropivacaine HCl solution) has been approved for surgical anesthesia and acute pain management in 40 countries.

The strength 5.0 mg/ ml is only approved and launched in Canada and USA.

The 7.5 mg/ ml preparation is approved for cesarean section in all countries, except in Canada and USA, where the 5.0 mg/ ml is recommended, and in Australia, where the use of Naropin® was not approved for the application cesarean section.

2. Marketing Approvals

Naropin® was first approved for marketing in Sweden on September 15, 1995. The approvals and launch dates are listed in Table 1.

3. Submissions

The original NDA for Naropin® is still under evaluation for approval as listed in Table 2.

This supplementary application has been or will be submitted in all countries, where Naropin® is approved today as listed in Table 1. It will also be submitted in the countries where Naropin® not yet is approved as soon as the marketing authorizations are granted.

4. Market Withdrawals

There have been no changes in the marketing status or labeling information for Naropin®. Naropin® has not been withdrawn from marketing in any country for any reason relating to safety or effectiveness. There are no significant problems with safety or effectiveness and no regulatory limitations have been imposed.

Table 1.

Marketing Status of NAROPIN ® Injection (July 7, 1998, Cut-off)

Country	Strength	Marketing approval year-month-day	Launch date year-month
Argentina	2.0, 7.5, 10 mg/ ml	1996-10-02	1997-04
Australia	-.-	1995-12-22	1996-05
Austria	-.-	1996-06-04	1997-01
Bahrain	-.-	1997-11-22	Not yet launched
Belgium	-.-	1996-08-21	1997-09
Brazil	-.-	1996-08-05	1997-04
Canada	2.0, 5.0, 7.5, 10 mg/ ml	1996-12-24	1997-04
Colombia	2.0, 7.5, 10 mg/ ml	1997-09-16	Not yet launched
Cyprus	-.-	1998-05-20	Not yet launched
Czech Republic	-.-	1997-12-03	Not yet launched
Denmark	-.-	1996-05-01	1996-05
Eire	-.-	1996-06-26	1997-01
Estonia	2.0 mg/ ml	1997-08-22	Not yet launched
Finland	2.0, 7.5, 10 mg/ ml	1995-10-09	1996-03
France	-.-	1996-08-20	1997-09
Germany	-.-	1996-08-14	1997-01
Greece	-.-	1996-09-27	Not yet launched
Holland	-.-	1995-10-03	1996-03
Hong Kong	-.-	1998-03-12	Not yet launched
Iceland	-.-	1998-03-01	1998-03
Israel	-.-	1997-08-10	Not yet launched
Italy	-.-	1996-10-10	1997-04
Kuwait	-.-	1997-06-01	Not yet launched
Lithuania	-.-	1997-03-21	Not yet launched
Luxemburg	-.-	1996-06-05	1997-06
Malaysia	-.-	1998-04-10	Not yet launched
Mexico	-.-	1998-03-30	1998-06
New Zealand	-.-	1996-05-30	1996-10
Norway	-.-	1997-05-16	1997-08
Philippines	-.-	1997-04-17	1998-01
Portugal	-.-	1996-12-31	1997-09
Romania	-.-	1998-05-01	Not yet launched
Singapore	-.-	1997-04-04	1997-11
Spain	-.-	1996-07-18	1998-05
South Africa	-.-	1997-04-25	1998-03

Table 1. (cont.)

Country	Strength	Marketing approval year-month-day	Launch date year-month
Sweden	-.-	1995-09-15	1996-04
Switzerland	-.-	1997-02-27	1997-06
UAE	-.-	1997-11-05	Not yet launched
United Kingdom	-.-	1996-05-17	1997-01
USA	2.0, 5.0, 7.5, 10 mg/ ml	1996-09-24	1996-10

Table 2.

Submission Status of NAROPIN ® Injection (July 7, 1998, Cut-off)

Country	Strength	Submission Date year-months-day
China	2.0, 7.5, 10 mg/ ml	
Hungary	-.-	
Indonesia	-.-	
Peru	-.-	
Poland	-.-	
Russia	-.-	
Saudi Arabia	-.-	
Taiwan	-.-	
Thailand	-.-	

Item 3

D. CMC SUMMARY

Naropin (ropivacaine HCl) was approved in the United States on September 24, 1996. The manufacture of Naropin solutions is identical to that previously described in approved NDA 20-533 for drug products contained in glass vials, ampules and infusion bottles.

6 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.