In light of the preclinical dose ranging teratology studies which show that ropivacaine crosses the placental barrier to reach the fetal circulation in pregnant rabbits, support exists for a cause and effect relation between the reported fetal serious adverse events and ropivacaine exposure.[13]

Uncontrolled Clinical Studies

In the uncontrolled studies patients were given 0.75% ropivacaine exclusively. In Study M4 (N=37) three (8%) serious adverse events were reported, i.e., pyloric stenosis, cleft palate and neonatal tachypnea. In Study M8 patients received either 150 mg (N=8) or 187.5 mg (N=8) of ropivacaine. No serious adverse event was reported because hypotension and bradycardia were not considered to be serious adverse events. They did occur in this trial however and with an incidence of 69% (11/16) and 6% (1/16) respectively. Hypotension was more common in the 187.5-mg ropivacaine exposed group.

All Studies Combined

Of the total three hundred and seventeen ropivacaine –exposed patients, thirty-five (35/317=11%) serious adverse events were reported in the ropivacaine exposed group (versus thirty-six (36/218=16%) serious adverse events following bupivacaine exposure. Due to the total number of related serious adverse events not being provided, compilations which include atypical serious adverse events, i.e., those not associated with local anesthetic administration such as cleft palate, in the total number of events leads to misinterpretation of the relationship between cause and effect.

[13] Goheer, A. "Review and Evaluation of Pharmacology and Toxicology Data", 5/18/99, p. 70

Table 84. Serious Adverse Events– All Cesarean Section Trials

Serious Adverse Event Listing Cesarean Section Ropivacaine Treatment					
Trial	**Patient**	**Age (years)**	**Dose**	**Adverse Event**	**Outcome/ Withdrawal**
M9 (n=124)	232	29	Ropivacaine 0.75% (188 mg)	Low APGAR Score	Recovered
	234	31	Ropivacaine 0.75% (150 mg)	Low APGAR Score	Recovered
	39	37	Ropivacaine 0.75% (150 mg)	Low APGAR Score	Still Present
				Neonatal Asphyxia	Recovered
	102	31	Ropivacaine 0.75% (150 mg)	Hypotension	Recovered
				Hypotension	Still Present
				Fetal Bradycardia	Improved
				Fetal Bradycardia	Recovered
	12	39	Ropivacaine 0.75% (150 mg)	Neonatal Jaundice	Improved
	24	20	Ropivacaine 0.75% (188 mg)	Neonatal Infection	Improved
	201	27	Ropivacaine 0.75% (150 mg)	Neonatal Fever	Recovered
	30	23	Bupivacaine 0.5% (100 mg)	Dizziness (suspected intravascular injection)	Recovered
M10 (n=116)	115	31	Ropivacaine 0.75% (150 mg)	Hypotension	Recovered
				Fetal Bradycardia	Recovered
				Ventricular Arrhythmia	Recovered
				Tachycardia	Recovered
	123	31	Ropivacaine 0.75% (150 mg)	Skin Disorder	Recovered
	611	31	Ropivacaine 0.75% (188 mg)	Neonatal Jaundice	Recovered

Serious Adverse Event Listing Cesarean Section Ropivacaine Treatment (continued)					
Trial	**Patient**	**Age (years)**	**Dose**	**Adverse Event**	**Outcome/ Withdrawal**
M11 (n=122)	101	28	Ropivacaine 0.75% (188 mg)	Postoperative Complications	Recovered
	123	31	Ropivacaine 0.75% (150 mg)	Neonatal Hypoglycemia	Recovered
				Respiratory Disorder	
				Neonatal Tachypnea	
	220	38	Ropivacaine 0.75% (188 mg)	VSD	Improved
	326	26	Ropivacaine 0.75% (188 mg)	Congenital Anomaly	Still Present
				Neonatal Asphyxia	Improved
	327	29	Ropivacaine 0.75% (150 mg)	Congenital Anomaly	Still Present
M12 (n=120)	218	29	Ropivacaine 0.75% (188 mg)	Neonatal Asphyxia	Recovered
				Vaginal Hemorrhage	Recovered
				Neonatal Pneumonia	Improved
M4 (n=32)	6	27	Ropivacaine 0.75% (225mg)	Neonatal Tachypnea	Recovered
	22	32	Ropivacaine 0.75% (150 mg)	Cleft Palate	Still Present
	26	35	Ropivacaine 0.75% (150 mg)	Pyloric Stenosis	Recovered

8.1.2.2 Discontinuations Due to an Adverse Event

No discontinuations due to an adverse event occurred in these studies. The instances where study drug was determined to be ineffective, for example, resulted in the administration of alternative therapy.

8.1.2.3 Overall Adverse Event Profile

8.1.2.3.1 *Distribution According to Organ Class*

Controlled Clinical Trials

The incidences of unique adverse events were compared and the data was pooled according to organ system.

The organ systems with the highest incidence of adverse events are those typically affected by local anesthetics, i.e., cardiovascular (hypotension: ropivacaine 49% and bupivacaine 52%), gastrointestinal (nausea: ropivacaine 25% and bupivacaine 26%), and skin and appendages (pruritus: ropivacaine 14% and bupivacaine 12%). These findings are consistent with the data in the original NDA trials comparing ropivacaine 0.5% to bupivacaine 0.5% for cesarean section. All other organ systems were effected less than 10%. Please note Appendix 9 for sponsor's Table (Appendix) 9-2, "The distribution of unique adverse events in the ropivacaine and bupivacaine groups....", item 8, vol. 106, p. 99-112.

Uncontrolled Clinical Trials

The data from patients exposed to ropivacaine alone showed similar results to the comparative trials, i.e., gastrointestinal disorders (nausea: M4 – 56%, M8 – 25%), cardiovascular (hypotension: M4-69%, M8-44%) were the leading organ systems affected.

All Studies Combined

The data from all studies combined showed the same trends: gastrointestinal disorders and cardiovascular were the leading organ systems affected.

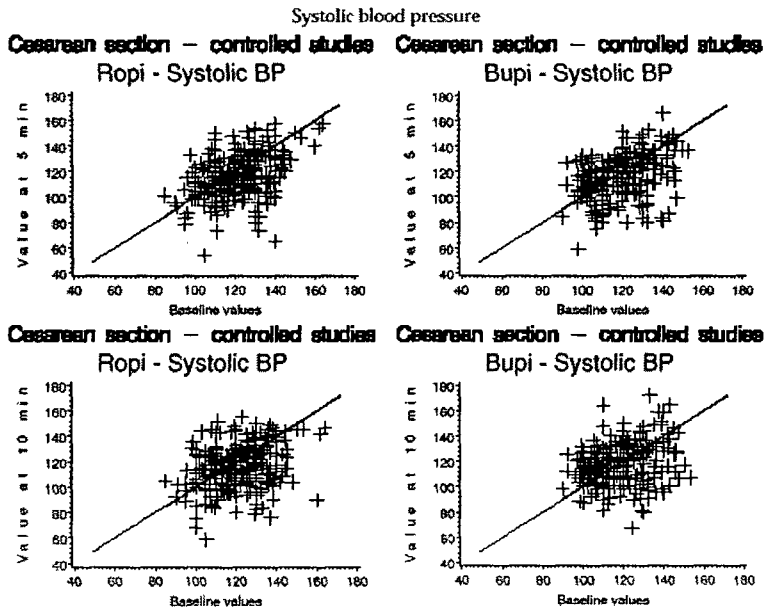
Outlier Analysis of Adverse Events - Blood Pressure and Pulse Rate

The administration of local anesthetics to parturients can be detrimental to both the mother and the fetus; typically, however, parturients and their fetuses do quite well. In special circumstances, i.e., technical complications, high risk patients and idiopathic conditions, untoward side effects can occur typically due maternal hypotension and bradycardia and consequently fetal complications. Therefore, an analysis of outliers is especially useful in determining the safety of 0.75% ropivacaine in obstetrics.

The sponsor has provided a series of comparative scatter plots of blood pressure and pulse rates that have proven to be quite useful in identifying outliers. The plots compare systolic and diastolic blood pressures and pulse rate at baseline to those at various time intervals, i.e., 5 minutes – 300 minutes post exposure to 0.75% ropivacaine or 0.5% bupivacaine.

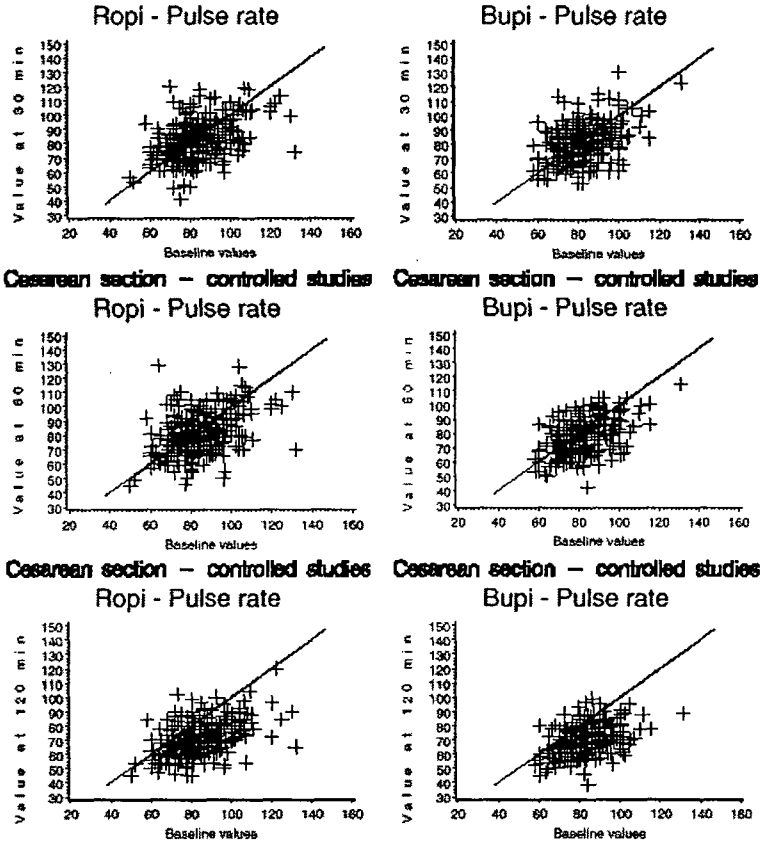
The results showed that there were several people who experienced very dramatic changes in blood pressure and heart rate and these changes were similar between treatment groups. Below please find representative scatter plots.

Table 85. Systolic BP - Scatter Plots



[Item 8, Vol. 106, p. 191]

Table 86 Pulse Rate – Scatter Plots



[Item 8, Vol. 106, p. 191]

In conclusion, there appeared to be no significant differences between ropivacaine and bupivacaine exposed patients in the incidence of outliers. Appropriately, the label for both of these products reflects their potential to elicit hypotension and bradycardia, However, there is a need to inform the practitioner of the potential for **severe** hypotension and bradycardia in a few outlying obstetric patients exposed to ropivacaine 0.75% for cesarean section.

8.1.2.4 OTHER ADVERSE EVENTS

8.1.2.4.1 *Adverse Events by Age*

All obstetric patients were within the same age range, i.e., 18-48. No specific age - related adverse event analysis was performed.

8.1.2.4.1 *Adverse Events by Gender*

All obstetric patients were the same sex. No gender specific adverse event analysis was performed.

8.1.2.5 Other Safety Findings

8.1.2.5.1 *Clinical Laboratory Evaluations*

Upon review of the clinical laboratory results for all obstetric studies, e.g., chemistry, hematology, ECG, vital signs, etc. found in integrated summary of safety, narrative summaries and case report forms and tabulations all abnormalities seen were predictable, transient and without obvious sequelae.

8.1.2.5.2 *Drug-Drug Interaction*

No data was submitted.

8.1.2.5.3 *Interaction with Antihypertensives*

No data was submitted.

8.1.2.6 Summary of Potential Adverse Events Considered Related to Study Drug

While the number of serious adverse event was statistically small, applying statistical significance as a criteria for clinical relevance may not be appropriate for such a small study population.

The relative severity of serious adverse events that occurred in patients exposed to appropriately administered 0.75% ropivacaine, i.e., maternal arrhythmia, maternal hypotension, fetal hypotension, fetal bradycardia, fetal asphyxia, low APGAR scores, following 0.75% ropivacaine versus the one episode of dizziness following accidental intravascular injection of bupivacaine, lends support for the assumption that the higher dosage of ropivacaine (0.75% ropivacaine versus 0.5% bupivacaine) is the explanation for the difference in serious adverse events.

Additional support for this conclusion is found in the preclinical data. According to the pharmacology reviewer, Dr. A. Goheer[14], "Toxicity in general is less with ropivacaine than with equivalent doses of bupivacaine. With high IV doses"...however..." this drug [ropivacaine] will produce cardiovascular toxicity similar to that reported for bupivacaine." and, " ...with a higher dose, 23 mg/kg, an increased pup [rabbits and rats] loss was seen...due to maternal toxicity."

[14] Goheer, A. "Review and Evaluation of Pharmacology and Toxicology Data", 5/18/99, p. 74-75.

8.1.3 Brachial Plexus Block (Studies P11 and P12)

Studies P11 and P12 are double blind randomized parallel group studies in which patients who are scheduled to undergo surgery of the hand or arm undergo either a subclavian perivascular brachial plexus block or axillary brachial plexus block with either 0.75% ropivacaine (in doses up to 300 mg) or 0.5% bupivacaine (in doses up to 200 mg). These studies are submitted in support of the proposed dosage recommendation of up to 40 ml of ropivacaine 7.5 mg/ml for major nerve block.

A total of two hundred and two patients (total N=202) underwent a brachial plexus block in the two controlled clinical trials (Studies P11 and P12) conducted, of which one hundred and two (**ropivacaine N=102**) were exposed to ropivacaine 0.75% versus one hundred (**bupivacaine N=100**) exposed to 0.5% bupivacaine.

Additionally, an uncontrolled dose ranging study (**Study P10** N=14) with 225 mg, 262.5 mg or 300 mg of 0.75% ropivacaine was conducted. This study was not submitted in support of any indication; however it will be analyzed for its contribution to the safety database.

Therefore, the total drug exposure in the brachial plexus block clinical trials is 116 patients exposed to ropivacaine and to 100 exposed to bupivacaine.

The analysis of adverse events has been conducted on pooled data from these two brachial plexus block studies. The following review will be based upon this pooled data.

8.1.3.1 Serious Adverse Events

There were a total of sixteen events classified as serious adverse events in the two controlled brachial plexus clinical trials (N=202). Ropivacaine and bupivacaine behaved similarly in these clinical trials. The organ system most commonly effected was "body as a whole"(ropivacaine 2/102=2% and bupivacaine 4/100=4%). This category includes the following events: pain (2/6: ropivacaine n=1 and bupivacaine n=1), postoperative complications (2/6, ropivacaine n=1 and bupivacaine n=1), and edema (2/6, bupivacaine n=2).

The second most common organ systems effected was equally "CNS" and "resist mechanisms". CNS (ropivacaine 2/102=2% and bupivacaine 2/100=2%) included the following events: convulsions (bupivacaine n=1 and ropivacaine n=1), neuropathy (bupivacaine n=1), syncope (ropivacaine n=1) and speech disorder (r n=1). Resist mechanisms (ropivacaine n=2 and bupivacaine n=2) for which the preferred term was infection.

A more meaningful compilation of data is one that focuses on those events typical of local anesthetics. Such an analysis is found below in the Section 8.1.4.2 Significant Adverse Events.

Case Narratives

Two case narratives were provided, both describe accidental intravascular injections:

I. Four minutes following a subclavian perivascular brachial plexus block with 0.5% **bupivacaine** (150 mg), a 30-year-old male (patient 314) had a "severe grand mal seizure" He was treated with an oral airway, manual ventilation, and 6 mg of midazolam. The patient regained consciousness and spontaneous ventilation approximately 30 minutes later without apparent sequelae.

II. Two minutes after receiving 0.75% **ropivacaine** (300 mg) via axillary block, patient 505 was noted to have "speech problems" and subsequent loss of consciousness and seizure activity lasting five minutes. The patient was treated with oxygen and diazepam and was said to have recovered without sequelae. He later completed his scheduled surgery under general anesthesia.

8.1.3.2 *Significant Adverse Event*

Interestingly, pooling of events coded as "significant" adverse events more accurately identifies those events likely to be drug related, i.e., it eliminated events not typical of local anesthetics such as cellulitis, wrist edema, etc. It also allowed the addition of patients (patients 221, 509 and 328) who, despite experiencing central nervous system toxicity, were excluded from the "serious" adverse events database.

Readily apparent from Table 87 below, there is a four-fold increase in the incidence of toxicity following exposure to ropivacaine 0.75% than following exposure to 0.5% bupivacaine. One can say with reasonable certainty that this difference in toxicity is not because bupivacaine is incapable of causing syncope, bradycardia, convulsions, or coma but that it was administered at a dose less likely to cause these events, i.e., concentration effect. Please note the table below.

Table 87. Significant Adverse Events (adapted from Sponsor's Table 7-7; 7 patients, 10 events Item 8, vol. 105, p. 369)

Organ Class	Ropivacaine N=102 n (%)	Bupivacaine N=100 n (%)	Preferred Term (Verbatim)
CNS	2 (2%)	0	Dizziness
CNS	1 (1%)	0	Speech Disorder
CNS	1 (1%)	1 (1%)	Convulsions
CNS	1 (1%)	0	Coma (loss of consciousness)
CNS	1 (1%)	0	Twitching (uncoordinated muscle contractions)
Cardiovascular	1 (1%)	1 (1%)	Syncope
Heart Rate	1 (1%)	0	Bradycardia
Total	**8 (8%)**	**2(2%)**	**10 (5%)**

[

8.1.3.3 Discontinuations Due to an Adverse Event

In addition to the two patients described above as having serious adverse events, two patients (Study P12) were discontinued secondary to an adverse event. The discontinuations described are in fact a temporary cessation of study drug administration; both patients subsequently completed therapy and all safety measurements.

Patient 509 experienced bradycardia (HR=45), muscle twitching and temporary loss of consciousness post-injection of study drug [Note: the name of the drug administered is pending a response from the sponsor]. The patient recovered without intervention and subsequently completed the axillary block procedure successfully. Patient 320 experienced also experience bradycardia in addition to dizziness and hypotension for which drug administration [Note: the name of the drug administered is pending a response from the sponsor] was temporarily discontinued. The patient was treated successfully with ephedrine and atropine and went on to complete all measurements.

8.1.3.4 Overall Adverse Event Profile

8.1.3.4.1 *Distribution According to Organ System*

When pooling all brachial plexus trials, the number of ropivacaine exposed patients increases from N=102 to N=116 with no corresponding change in the number of bupivacaine exposed patients. The contribution made by the addition of Study P10 (N=14) did not significantly effect the overall adverse event profile.

The adverse events with the highest overall incidence in decreasing order of frequency are nausea (ropivacaine 25%, bupivacaine 16%), pain (ropivacaine 8%, bupivacaine 7%) and hypoanesthesia (ropivacaine 4%, bupivacaine 8%).

Distribution of Unique Adverse Events ≥ 5%: **Comparative** Brachial Plexus Block Trials (based upon Sponsor's Table (Appendix) 10-2)

EVENT	**Ropivacaine** N=105 N %	**Bupivacaine** N=102 N %
CNS and PNS Disorders		
Hypoaesthesia	4 (4)	8 (8)
Dizziness	6 (6)	0
Gastrointestinal Disorders		
Nausea	26 (25)	16 (16)
Vomiting	5 (5)	7 (7)
Body as a Whole		
Pain	8 (8)	7 (7)
Peripheral Edema	3 (3)	5 (5)
Cardiovascular Disorders, general		
Hypotension	1 (1)	4 (4)
Heart Rate and Rhythm Disorders		
Bradycardia	2 (2)	4 (4)
Resistance Mechanism Disorders		
Infection	6 (6)	2 (2)
Fever	1 (1)	0

Comparative Distribution of Adverse Events ≥ 5%:
All Brachial Plexus Block Trials (based upon Sponsor's Table (Appendix) 10-9)

EVENT	Ropivacaine **(includes data from noncomparative trial)** N=119 N %	Bupivacaine N= 102 N %
CNS and PNS Disorders		
Hypoaesthesia	4 (3)	8 (8)
Dizziness	6 (5)	0
Total	28	18
Gastrointestinal Disorders		
Nausea	26 (22)	16 (16)
Vomiting	5 (4)	7 (7)
Total	33	23
Body as a Whole		
Pain	8 (7)	7 (7)
Peripheral Edema	3 (3)	5 (5)
Total	18	22
Resistance Mechanism Disorders		
Infection	6 (5)	2 (2)
Total	6	2
Fever	1 (1)	0

8.1.3.5 OTHER ADVERSE EVENTS

8.1.3.5.1 *Adverse Events by Age*

The ages of the patients in the brachial plexus block trials were 19-76 years old. Patients <40 years of age made up 30% (ropivacaine 34% and bupivacaine 28%) of the study population, those 40-64 years of age made up 50% (ropivacaine 50% and bupivacaine 51%) of the population and those >64 years of age made up 20% (ropivacaine 16% and bupivacaine 21%) of the population. Therefore, conclusions based upon age <65 (75% of the study population) versus age >65 (25% of the study population) would be difficult.

One can conclude that the adverse event which occurred in patients greater than 65 were those typical of aging not of local anesthetics, in the majority of cases, e.g., arthropathy, confusion. Additionally, elderly patients complained of similar adverse event as their younger counterpart, e.g., nausea (<65-25%, >65 – 24%). Surprisingly, headache was a relatively common (12%) complaint among elderly patients.

In conclusion, the data provided supports the conclusion that increasing age was not associated with increasing numbers of adverse events in patients receiving a brachial plexus block and patients were not more apt to experience an adverse event if they were >65 years of age.

8.1.3.5.1 *Adverse Events by Gender*

The ratio of males to females study participants was 60% to 40%, respectively. Notably, in the ropivacaine group, females had disproportionately more complaints of nausea (female 43%, male 13%), pain (female 12%, male 5%), dizziness (female 10%, male 3%) and peripheral edema (female 11%, male 2%) than males. This same trend was seen in the bupivacaine group. However, overall there were equal numbers of adverse events occurring between sexes and treatment groups.

8.1.3.6 Other Safety Findings

8.1.3.6.1 *Clinical Laboratory Evaluations*

Upon review of the clinical laboratory results for both brachial plexus trials, e.g., chemistry, hematology, ECG, vital signs, etc. found in integrated summary of safety, narrative summaries and case report forms and tabulations, abnormalities seen were predictable, transient and without obvious sequelae.

8.1.3.6.2 *Drug-Drug Interaction*

No data was submitted to address this issue.

8.1.3.6.3 *Interaction with Antihypertensives*

No data was submitted to address this issue.

8.1.3.7 Summary of Potential Adverse Events Considered Related to Study Drug

As seen previously in the cesarean section trials, 0.75% ropivacaine is associated with an increased risk for serious adverse events over those associated with 0.5% bupivacaine. While the number of serious adverse event was statistically small, applying statistical significance as criteria for clinical relevance may not be appropriate for such a small study population.

Of special interest is the comments made by the pharmacokinetic reviewer, "...ropivacaine plasma concentration in some patients may approach the threshold for central nervous system toxicity, after 300 and 375 mg [40 and 50 ml of 0.75% ropivacaine] infiltration...or 300 mg [40 ml of 0.75% ropivacaine] brachial block." This information further supports limiting the administration of 0.75% ropivacaine by these routes of administration.

Clinically, it is not uncommon for clinicians to need to give an extra 5, 10 even 15 ml of local anesthetic to ensure adequate block. For example, when conducting a closed infiltration block, in which your only indication of location of the needle tip is the number of "pops" felt as you advance the needle, one can often need to give additional milliliters of local anesthetic due to suspected miscalculation of needle location.

This is also true of the brachial plexus block due to the anatomy of the plexus, i.e., certain nerves need supplemental injections to ensure adequacy of certain dermatomal distributions. Therefore, by limiting use to only the 0.5% ropivacaine concentration, a wider safety margin exists allowing for these not uncommon and often necessary additional doses of local anesthetic.

8.1.3.8 Postoperative Pain Management

8.1.3.8.1 Other Serious Adverse Events

Ropivacaine versus Ropivacaine + Fentanyl

The analysis of adverse events will be conducted on pooled data from all postoperative pain management studies conducted. However, **Studies 010 and 011** that are identified as "...the main component of the clinical study program", will undergo a combined review.

Additionally, the postoperative pain management trials will be further separated according to the active comparator employed. This is done in light of the fact that the active comparator in many trials was ropivacaine (with a narcotic). The separation out of trials in which the comparator was not ropivacaine, e.g., bupivacaine or PCA morphine, allows the review of this more relevant data.

Table 88. Overall Study Design – Study 010 (adapted from Sponsor's Table 8-1 and 8-2)

STUDY 010	**SURGERY**	**POSTOPERATIVE 72 HOUR INFUSION**
GROUP 1	General Anesthesia + 0.75% Ropivacaine Epidural Block	Continuous ropivacaine (2 mg/ml) epidural infusion ± ketorolac
GROUP 2	General Anesthesia + 0.75% Ropivacaine Epidural Block	Continuous ropivacaine (2 mg/ml) + fentanyl 2 ug/ml epidural infusion ± ketorolac
STUDY 011	**SURGERY**	**POSTOPERATIVE 72 HOUR INFUSION**
GROUP 1	General Anesthesia + 0.75% Ropivacaine Epidural Block	Continuous ropivacaine (2 mg/ml) epidural infusion ± acetaminophen
GROUP 2	General Anesthesia + 0.75% Ropivacaine Epidural Block	Continuous ropivacaine (2 mg/ml) + fentanyl 1 ug/ml epidural infusion ± acetaminophen
GROUP 3	General Anesthesia + 0.75% Ropivacaine Epidural Block	Continuous ropivacaine (2 mg/ml) + fentanyl 2 ug/ml epidural infusion ± acetaminophen
GROUP 4	General Anesthesia + 0.75% Ropivacaine Epidural Block	Continuous ropivacaine (2 mg/ml) + fentanyl 4 ug/ml epidural infusion ± acetaminophen

"In-patient hospitalization or prolongation of existing in-patient hospitalization" (ropivacaine N=15/141, ropivacaine + fentanyl 2 ug/ml N=31/136) due to gastrointestinal disorders (ropivacaine n=5 and ropivacaine + 2fentanyl n=21) was the most frequently occurring serious adverse event. The second most common event was "medical or surgical intervention to prevent permanent impairment of function or permanent damage to a body structure" (ropivacaine N=7/141, ropivacaine + fentanyl 2ugml N=11/136).

The majority of organ system events resulting in prolonged hospitalization were gastro-intestinal system disorders (ropivacaine n=5 and ropivacaine + 2fentanyl n=21) which includes such events as dyspepsia and hemetemesis, followed by "body as a whole- general disorder" (ropivacaine n=8 and ropivacaine +2fentanyl n=10) Here again we see that the addition of fentanyl increased the incidence of adverse events, however, in this case it doubled the incidence. Please note "Overall Adverse Event Profile" for the specific organ system involvement across postoperative pain management trials.

When analyzing Studies 010 and 011, in which patients in both treatment groups received ropivacaine, the incidence of serious adverse events with increasing duration of infusion is the relevant data to analyzed, i.e., with respect to the proposed changes. As illustrated in the table below, the incidence of adverse events did not significantly change with increasing duration of infusion over 70 hours. The addition of fentanyl to the drug regimen increased the incidence of serious adverse events.

Table 89. Overview of Serious Adverse Events Occurring ≥ 5%– Ropivacaine versus Ropivacaine + 2Fentanyl By Treatment Duration

ORGAN CLASS	ROPIVACAINE		ROPIVACAINE + 2 FENTANYL	
	70H (N=83)	<70H (N=58)	70H (N=90)	<70H (N=46)
Body as a Whole	11%	14%	12%	
Gastrointestinal System Disorders	5%	9%	37%	22%
Respiratory System Disorders	0	3%	9%	9%
Urinary System Disorders	0	0	2%	11%

[Item 8, Vol. 106, p. 38]

*Ropivacaine versus Bupivacaine (**Study 012**)*

The comparative incidence of serious adverse events between those patients exposed to ropivacaine (11%) versus those exposed to bupivacaine (26%) is hampered by the small sample size, i.e., ropivacaine (N=27) and bupivacaine (N=27). It is difficult therefore to make definitive conclusions based upon only 54 patients.

Table 90. Overview of Serious Adverse Events – Ropivacaine versus Bupivacaine

Study	Drug	No. of Patients n	No. of Patients with AE n (%) [u[16], a]	No. of deaths n (%)	No. of SAE n (%) [u, a]	No. of Severe AE n (%) [u, a]	No. of pat. disc due to AE perm. stopped n (%)
Controlled studies - Ropi vs. Bupi.							
O12 94RO85	Ropi	27	22(81%) [55, 77]	0 (0%)	3 (11%) [3, 3]	0 (0%) [0, 0]	0 (0%)
	Bupi	27	23(85%) [65, 80]	0 (0%)	7 (26%) [8, 8]	3 (11%) [3, 3]	1 (4%)
Grand total	Total	54	45(83%) [120, 157]	0 (0%)	10 (19%) [11, 11]	3 (6%) [3, 3]	1 (2%)

[Item 8, vol. 106, p. 17]

Ropivacaine + PCA Morphine versus PCA Morphine Alone

In all three trials, the incidence of serious adverse events was higher in the ropivacaine group than in the PCA morphine group. Interestingly, the incidence of serious adverse events decreased with the addition of PCA morphine to ropivacaine.

Study 013 (N=96) – ropivacaine (31%) versus ropivacaine + PCA morphine (14%) versus PCA morphine alone (17%),
Study 014 (N=130)– ropivacaine (18%) versus ropivacaine + PCA morphine (11%) versus PCA morphine alone (15%),
Study 015 (N=88) – ropivacaine (9%) versus PCA morphine (7%).

The specific types of serious adverse events occurring in the ropivacaine versus PCA morphine trials can be seen in the table below.

Table 91. Distribution of Unique Adverse Events – Ropivacaine versus PCA Morphine – Incidence >10% (adapted from sponsor's table 11.1.3.1 see Appendix 5 for further details)

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(40)
Urinary Tract Infection	8(7)	15(18)	6(5)
Postoperative Complications	19(16)	15(18)	22(17)
Pruritus	7(6)	11(13)	8(6)

As illustrated above, nausea and hypotension were the leading serious adverse events, followed by fever and pain. Interestingly, headache was three and five times more likely in the PCA morphine group than in the ropivacaine and ropivacaine + PCA morphine groups, respectively.

"Other Studies" – Study I32 and Study 09

The sponsor has grouped two separate studies (Study I32 and Study 09) into one category entitled "other studies" implying the lack of overall relevance of these studies to the proposed changes in ropivacaine administration.

Study I32 (N=26)- "72 Hour Continuous Epidural Infusion with 20 and 30 mg/hour Ropivacaine 2 and 3 mg/ml for Postoperative Pain Relief Following Major Orthopaedic Surgery – A Pharmacokinetic and Clinical Evaluation")

Study 09 (N=11) -"Continuous 72 Hour Epidural Infusion of Ropivacaine for Pain Management After Orthopaedic Surgery – A Pharmacokinetic and Clinical Evaluation"

The incidence of serious adverse events occurring in **Study I32** was 6% in patients exposed to 2 mg/ml of ropivacaine (N=16) versus 0% in patients exposed to 3 mg/ml of ropivacaine (N=12). Due to the small sample size, no definitive conclusions can be drawn from this data.

In the open label, noncomparative, **Study 09**, the incidence of serious adverse events was 27% in the eleven evaluable patients. Notably, Study 09 was terminated secondary to a high incidence of pyrexia, the details of which can be found in the section titled, "Special Safety Evaluation – Fever". Please note Appendix 4.0 sponsor's Table 8-16. "Overview of adverse events in "other studies", item 8, vol. 106, p. 19.

8.1.3.9 Discontinuations Due to an Adverse Event

Ropivacaine versus Ropivacaine + Fentanyl

All patients in this trial were exposed to ropivacaine; therefore, the affect of increasing the duration of infusion to ≥ 70 hours on the rate of discontinuations is relevant data to analyze.

Surprisingly, in patients exposed to ≥ 70 hours of ropivacaine (**Study 010**), the incidence of discontinuations (protocol defined as permanent or temporary cessation of infusion) due to serious adverse events was 0% compared to 56% in those patients exposed to < 70 hours of ropivacaine. Additionally, the incidence of discontinuations due to serious adverse events in those patients exposed to ≥ 70 hours of ropivacaine + fentanyl 2 ug/ml was 2% vs. 65% in those patient exposed to < 70 hours of ropivacaine + fentanyl 2 ug/ml.

In **Study 011**, the same trend was duplicated, i.e., increased frequency of discontinuations due to serious adverse events in patients exposed to the shorter infusion duration and a contributory effect with the addition of fentanyl.

This surprising information may be explained by the fact that technical difficulties, e.g., insufficient block, catheter displacement, one-sided block, etc., which tend to occur soon after the start of the infusion was the leading reason for discontinuation.

With respect to the specific events leading to discontinuations, unexpected therapeutic effect (technical difficulties) was the leading reason for temporary and permanent discontinuations as well as dose changes.

Table 92 Adverse Event leading to Discontinuation – Studies 010 and 011(adapted from sponsor's table 8-19, vol. 106, p. 28-30).

EVENT	ROPIVACAINE N=141 n(%)	ROPIVACAINE +2FENTANYL N=136 n (%)	TOTAL
Unexpected Therapeutic Effect	15 (11)	11(8)	26
Hypotension	2(1.4)	3(2)	5

*Ropivacaine versus Bupivacaine – **Study 012***

The was a slight increase in the incidence of discontinuations due to an adverse event between those exposed to ropivacaine (0%) versus those exposed to bupivacaine (4%). However, because only 54 patients were enrolled in this study, no definitive conclusions can be drawn. Please note in Appendix 2.0 Sponsor's Table 8-14. "Overview of adverse events, ropivacaine vs. bupivacaine comparison."

Ropivacaine + PCA Morphine versus PCA Morphine Alone

In all cases, ropivacaine alone was associated with the highest incidence of discontinuations due to an adverse event. As was also true of the incidence of serious adverse events, the addition of PCA morphine to the study regimen did not have an additive effect on the incidence of discontinuations secondary to an adverse event. Please note in Appendix 3.0 Sponsor's Table 8-15 "Overview of adverse events, ropivacaine vs. ropivacaine + PCA vs. PCA alone.".

Study 013 (N=96)- ropivacaine (13%) versus ropivacaine + PCA morphine (0%) versus PCA morphine alone (3%),
Study 014 (N=130)- ropivacaine (5%) versus ropivacaine + PCA morphine (2%) versus PCA morphine alone (2%),
Study 015 (N =88) – ropivacaine (0%) versus PCA morphine (0%).

Table 93. Discontinuations due to an Adverse Event (adapted from sponsor's table 8-20, vol. 106, p. 30)

EVENT	ROPIVACAINE (N=65) n(%)	PCA MORPHINE (N=81) n	ROPIVACAINE + PCA MORPHINE (N= 80) n
Hypotension	2(3)	0	0
Sciatica	1(1.5)	0	0
Bradycardia	1(1.5)	0	0
ECG Changes	1(1.5)	0	0
Postoperative Pain	1(1.5)	0	0
Confusion	0	1(1.2)	0
Respiratory Depression	1(1.5)	0	0
Surgical Complications	1(1.5)	0	0
Hemorrhage	0	1(1.2)	1(1.2)
Total	8(12)	2(2.4)	1(1.2)

*"Other" Studies - **Study I32 and Study 09***

The sponsor has pooled data from two separate studies (Study I32 and Study 09) and has defined this category as "other studies". Notably, Study 09 was terminated prematurely secondary to a high incidence of pyrexia.

The incidence of serious adverse events occurring in **Study I32** ("72 Hour Continuous Epidural Infusion with 20 and 30 mg/hour Ropivacaine 2 and 3 mg/ml for Postoperative Pain Relief Following Major Orthopaedic Surgery – A Pharmacokinetic and Clinical Evaluation") was 6% in patients (N=16) exposed to 2 mg/ml of ropivacaine versus 0% in patients (N=12) exposed to 3 mg/ml of ropivacaine. No definitive conclusions can be drawn based upon such a small sample size. The adverse events however were similar to that seen in the other larger trials.

In the open label **Study 09** ("Continuous 72 Hour Epidural Infusion of Ropivacaine for Pain Management After Orthopaedic Surgery – A Pharmacokinetic and Clinical Evaluation"), the incidence of serious adverse events was 0% in the eleven evaluable patients. This trial is the subject of a special safety evaluation, please see the section titled, "Special Safety Evaluation – Fever"

Please note Appendix 4.0 sponsor's Table 8-16. "Overview of adverse events in "other studies"

No data has been provided of the incidence of discontinuations due to serious adverse events for all postoperative pain management studies combined.

Study 09

"Continuous 72-hour Epidural Infusion of Ropivacaine for Pain Management after Orthopaedic Surgery – A Pharmacokinetic and Clinical Evaluation"

Study 09 was an open labeled study conducted by a single investigator in Australia in which American Society of Anesthesiologists physical status I-III [ASA I (N=3), ASA II (N=3), ASA III (N=4)] male and female patients age 21-74, received a continuous infusion of 2 mg/ml ropivacaine in doses up to 14 ml/hour for 72 hours following major orthopedic surgery.

Fifteen patients were enrolled, eleven of which were evaluable for safety. Of these eleven completing patients, all eleven developed fever (protocol defined as temperature above 38.5°C). All of the fevers occurred after the start of the infusion and the majority of patients had recurrent febrile episodes despite treatment with acetaminophen (1 gram). The frequency with which the fevers occurred prompted trial termination.

The patients suffered from multiple other side effects including hypotension (10/11), anemia (9/11), headache (8/11), bradycardia (6/11), chills (5/11) and urinary retention (5/11).

The sponsor has concluded that the etiology of the febrile episodes were in the majority of cases underlying infection, e.g., respiratory, knee, chest, etc. and has provided Table 27 (below) to detail the event, treatment, possible cause, and temporal relationship to study drug infusion. However, this reviewer looks to a concentration effect etiology. Of all the trials performed, this was the only trial in which patients were exposed to the highest available concentration of ropivacaine, i.e., 10 mg/ml.

The unusually high incidence of post continuous infusion pyrexia was noted by the medical reviewer in the original NDA safety update, "Fever ≥ 38.5° C continues to be observed and remains a dose-dependent issue during continuous...[ropivacaine]...epidural infusions for analgesia[15].

From the data available, the common denominator among those patients with fever was, (1) exposure to the highest available dose of ropivacaine, (2) orthopedic surgery, (3) single investigator, and (4) single trial site. Of all these possible etiologies, the fact that fever occurred in 100% of patients exposed lends credence to either a drug – induced etiology, or investigator technique.

[15] NDA 20-533, "Medical Officer Safety Update Review" by Robert F. Bedford, M.D., August 4, 1996, (letter/submission date: July 16,1996)

Table 94. Time Course of and Patient- Specific Event of Fever

(Awaiting clarification from sponsor of comment "other reason than fever" - Patient 0002)

Patient number	Event of fever (preferred term), hours from start of infusion	Treatment, reason, acetaminophen 1 g and hours from start of infusion	Possible cause
0001	27h, 47h,	fever: 2 g at 50h, pain:73h	Respiratory infection
0002		other reason than fever: 19h, 28h, 36h, 48h, 58h, 68h, 74h	
0003		headache : 16h, 39h, 55h,	
0005	9h	pain: 32h, 47h	Unknown
0006	4h, 22h,	fever : 5h, 22h, 58 h, 67h,	Inflammation, localized rt cubital fossa
0007	30h, 48h, 51h,	headache :6h, back pain:13h, 22h, 32h wound pain :66h, 71h	
0008	4h, 8h, 29h, 37h, 47h, 57h, 71h	headache:21h, 28h, 42h fever 48h	Phlebitis
0009	18h, 33h, 38h,48h, 62h, 160h	fever : 25h, 40h, 48h, 70h	Chest infection
0011	12h, 34h, 48h, 60h, 68h,	headache: 18h fever:4g at 19h,	Knee infection
0012	7h	pain : 39h,	Pharyngitis
0013	6h, 16h, 20h, 33h, 78h,	headache: 2h, fever: 7h, 21h, pain: 45h, 93h	Wound infection

[Item 8, vol. 101, p.95]

Further investigation into all trials conducted with respect to this unusually high incidence of fever revealed the following.

Of the twenty trials performed, nine observed body temperatures ≥ 38.5. This number (nearly half) may in fact be much higher considering the fact that seven of the remaining eleven trials did not assess body temperature. However, without the temperature assessments from **all** comparative trials, it is difficult to judge whether ropivacaine may be the cause of these temperature elevations or not.

Despite the lack of complete data on all patients exposed to the 10 mg/ml concentration, it is prudent to inform the public of the possibility of post ropivacaine exposure febrile episodes. Clinicians may choose not to use this product in patients with preexisting fever, e.g., leukemia, sepsis, etc., if aware of this drugs potential to exacerbate the condition. Also, if clinicians are well informed, they may not diagnose a patient with "fever of unknown origin" needlessly.

8.1.3.10 Overall Adverse Event Profile – Postoperative Pain Management

No data has been provided of the overall incidence of adverse events for all postoperative pain management studies combined.

8.1.3.10.1 *Distribution According to Organ Class and Duration of Infusion*

The incidences of adverse events were compared by duration of infusion and the data was pooled across all postoperative pain management trials according to organ system. The relevance of this data is based upon the proposed increase in ropivacaine infusion from 24 to 72 hours postoperatively.

A clear separation of temporal effects can be seen in the following organ systems, where there is an increase in the incidence of adverse event with increasing duration of drug infusion:

(1) **Central and Peripheral Nervous System disorders** - two fold increase in incidence of adverse events in patients exposed to ≥ 70 hours of infusion,
(2) **Cardiovascular disorders, general** - ≤ two fold increase in incidence of adverse events in patients exposed to ≥ 70 hours of infusion,
(3) **Gastrointestinal System disorders** – 1:1.5 ratio of adverse events with increasing duration of study drug infusion
(4) **Urinary System disorders** - - two fold increase in incidence of adverse events in patients exposed to ≥ 70 hours of infusion

8.1.3.10.2 *Distribution According to Unique Adverse Event and Duration of Infusion*

Ropivacaine vs. Ropivacaine + 2 ug/ml Fentanyl (72 Hour Infusion)

The incidences of adverse events were compared by duration of infusion and the data was pooled according to unique adverse events. Please note the following table for the leading system-specific adverse events: The relevance of this data is based upon the proposed increase in ropivacaine infusion from 24 to 72 hours postoperatively.

Table 95. Distribution of Unique Adverse Events ≥ 10%: Ropivacaine vs. Ropivacaine + 2 ug/ml Fentanyl Postoperative Pain Management
(based upon Sponsor's Table (Appendix) 11-1, item 8, vol. 107, p.1)

EVENT	Ropivacaine N=141 N (%)	Ropivacaine + 2 ug/ml Fentanyl N=136 N (%)
CNS AND PNS DISORDERS:		
Dizziness:		
≥ 70 hour	24 (29)	27 (30)
< 70 hour	7 (12)	10 (22)
Hypoanesthesia:		
≥ 70 hour	9 (11)	4 (4)
< 70 hour	3 (5)	2 (4)
Gastrointestinal Disorders:		
Nausea:		
≥ 70 hour	54 (65)	55 (61)
< 70 hour	32 (55)	27 (59)
Vomiting:		
≥ 70 hour	28 (34)	31 (34)
< 70 hour	17 (29)	14 (30)
Diarrhea:		
≥ 70 hour	15 (18)	7 (8)
< 70 hour	8 (14)	8 (17)
METABOLIC AND NUTRITIONAL DISORDERS:		
Hypoproteinemia:		
≥ 70 hour	13 (16)	19 (21)
< 70 hour	11 (19)	5 (11)
Inc. Creatinine Phosphokinase*:		
≥ 70 hour	10 (12)	19 (21)
< 70 hour	10 (17)	6 (13)
Hypocalcemia:		
≥ 70 hour	11 (13)	13 (14)
< 70 hour	9 (16)	7 (15)
Hypokalemia:		
≥ 70 hour	9 (11)	14 (16)
< 70 hour	6 (10)	5 (11)
Decreased BUN:		
≥ 70 hour	2 (2)	6 (7)
< 70 hour	7 (12)	3 (7)
CARDIOVASCULAR DISORDERS, GENERAL:		
Hypotension:		
≥ 70 hour	62(75)	61(68)
< 70 hour	35(60)	35(76)

* Creatinine phosphokinase is an enzyme indicative of myocardial injury; therefore it would be more appropriately placed in the "Cardiovascular Disorders, general" category.

Table 96. Distribution of Unique Adverse Events ≥ 10%: Ropivacaine vs. Ropivacaine + 2 ug/ml Fentanyl Postoperative Pain Management (continued) (based upon Sponsor's Table (Appendix) 11-1, item 8, vol. 107, p.1)

EVENT	Ropivacaine N=141 N (%)	Ropivacaine + 2 ug/ml Fentanyl N=136 N (%)
CARDIOVASCULAR DISORDERS, GENERALM (continued)		
Hypertension:		
≥ 70 hour	12(14)	13(14)
< 70 hour	5(9)	5(11)
Hypotension, postural:		
≥ 70 hour	6(7)	6(13)
< 70 hour	2(3)	5(6)
URINARY SYSTEM DISORDERS:		
Oliguria:		
≥ 70 hour	32(39)	23(26)
< 70 hour	14(24)	14(30)
Hematuria		
≥ 70 hour	17(20)	23(26)
< 70 hour	9(16)	6(13)
Urine Abnormal:		
≥ 70 hour	8(10)	17(19)
< 70 hour	2(3)	6(13)
Pyuria:		
≥ 70 hour	10(12)	9(10)
< 70 hour	2(3)	4(9)
Albuminuria:		
≥ 70 hour	1(2)	3(7)
< 70 hour	6(7)	11(12)
Urinary Retention:		
≥ 70 hour	8(10)	7(8)
< 70 hour	1(2)	3(7)
RESPIRATORY SYSTEM DISORDERS:		
Hypoxia:		
≥ 70 hour	9(11)	10(11)
< 70 hour	6(10)	6(13)
Dyspnea:		
≥ 70 hour	9(11)	7(8)
< 70 hour	4(7)	2(4)
Pleural Effusion:		
≥ 70 hour	4(5)	7(8)
< 70 hour	3(5)	2(4)
Atelectasis:		
≥ 70 hour	3(4)	11(12)
< 70 hour	2(3)	2(4)
Fever:		
≥ 70 hour	23 (28)	32 (36)
< 70 hour	17 (29)	14 (30)

Notably, nausea is a warning sign of hypotension in patients exposed to the vasodilatory effects of local anesthetics. Therefore, it is plausible that the incidence of hypotension would more accurately be represented by some combination of the percentages of hypotension and nausea.

With respect to the proposed increase in duration of infusion from 24 to 72 hours, as can be seen from the data presented, increasing duration of drug infusion had a negative impact on the incidence of adverse events. In the majority of cases there was a two fold increase in the incidence of unique adverse events occurring in patients exposed to more than 70 hours of study drug infusion.

Also of special concern is the finding that the incidence of fever increased with increasing duration of study drug infusion – ropivacaine alone and ropivacaine with 2 ug/ml fentanyl and possibly with increasing concentration (Study 09). Notably, fever affected approximately 30% of patients.

Finally, the number of adverse events did not uniformly increase with the addition of narcotics, e.g., fentanyl 2 ug/ml , PCA morphine. In fact, there were many instances where the number of adverse events was higher in the ropivacaine alone group. Please note Appendix 5 sponsor's Table (Appendix) 11-14, item 8, vol. 107, p. 210 for ropivacaine versus ropivacaine + PCA morphine distribution of unique adverse events.

*Ropivacaine vs. Bupivacaine (**Study 012**)*

This study included only 54 patients; therefore, it is difficult to draw any definitive comparative conclusions from such a small sample size. The table below is presented however, for its contribution to the overall ropivacaine safety database. As can be seen the leading adverse events following ropivacaine exposure were nausea and hypotension.

Table 97. Distribution of Unique Adverse events

Organ System	Ropivacaine N=27 N (%)	Bupivacaine N=27 N (%)
Cardiovascular Disorders:		
Hypotension:	9 (33)	12.(44)
Gastrointestinal Disorders:		
Nausea:	11 (41)	9(33)
Body as a whole – general disorders:		
Fever:	4 (15)	5 (19)
Heart Rate and Rhythm Disorders:		
Bradycardia	2 (7)	4 (15)

Ropivacaine ± PCA Morphine vs. PCA Morphine Alone

As illustrated in the table below, in the majority of instances, ropivacaine and PCA morphine were associated with similar incidences of adverse events. However, ropivacaine was associated with a greater than two fold increase in the incidence of pain, back pain and headache over that of patients exposed to PCA morphine.

Table 98. Distribution of Unique Adverse Events – Ropivacaine vs. PCA Morphine (Incidence > 10%)

Organ System	Ropivacaine N=116 N (%)	Ropivacaine + PCA Morphine N=84 N (%)	PCA Morphine N=128 N (%)
Gastrointestinal Disorders:			
Nausea	53 (46)	40 (48)	62 (48)
Vomiting	34 (29)	24 (29)	42 (33)
Constipation	15 (13)	17 (20)	2 (16)
Cardiovascular Disorders:			
Hypotension:	56 (48)	49 (58)	51 (40)
Hypertension	15(13)	15 (18)	32 (25)
Heart Rate and Rhythm Disorders:			
Bradycardia	21(18)	8(10)	18(14)
Respiratory System Disorders			
Hypoxia	17(15)	19(23)	28(22)
CNS and PNS Disorders			
Headache	18(16)	6(7)	5(4)
Skin and Appendages Disorders:			
Pruritus	7(6)	11(13)	8(6)
Body as a whole – general disorders:			
Fever	32 (28)	33(39)	30(23)
Pain	35(30)	30(36)	26(20)
Postoperative Complications:	19(16)	15(18)	22(17)
Back pain	16(14)	6(7)	4(3)
Rigors (chills)	13(11)	4(5)	8(6)
Urinary System Disorders			
Urinary Tract Infection	8(7)	15(18)	6(5)
RBC Disorders			
Anemia	30(26)	17(20)	26(20)

8.1.3.11 OTHER ADVERSE EVENTS – Postoperative Pain Management[16]

No analysis was performed of patients exposed to ropivacaine versus bupivacaine or ropivacaine + PCA morphine with respect to age or gender.

8.1.3.11.1 *Adverse Events by Age*

In the ropivacaine versus ropivacaine + 2fentanyl trials, increasing patient age did not adversely influence events. In fact, in the majority of cases the incidence of adverse events decreased with increasing age.

The organ systems with the most adverse events were gastrointestinal and cardiovascular systems with frequencies greater than 60 % in both patients >65 and <65. Please see Appendix 6, "Table (Appendix) 11-4. Adverse events by age". Item 8, Vol. 107, p. 32-44."

8.1.3.11.2 *Adverse Events by Gender*

The distribution of adverse events was similar among males and females. Interestingly, in the category anemia, where one would expect more female contribution, there was in fact equal distribution of events from both males and females.

Please note Appendix 7 for the sponsor's Table (Appendix) 11-5, item 8, vol. 107, p. 45-57.

8.1.3.12 Other Safety Findings Postoperative Pain Management

8.1.3.12.1 *Clinical Laboratory Evaluations*

Upon review of the clinical laboratory results for all postoperative pain management studies, e.g., chemistry, hematology, ECG, vital signs, etc. found in integrated summary of safety, narrative summaries and case report forms, case report tabulations, abnormalities seen were predictable, transient and without obvious sequelae. Please note Section 8.1.2.3.1 Special Safety Evaluation – Fever.

8.1.3.12.2 Drug-Drug Interaction

No data was submitted.

8.1.3.12.3 Interaction with Antihypertensives

No data was submitted.

8.1.3.12.4 *Summary of Potential Adverse Events Considered Related to Study Drug - Postoperative Pain Management*

Please note Section 8.1.2.3.1 Special Safety Evaluation - Fever

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[16] Note: data submitted for ropivacaine versus ropivacaine + fentanyl only.

8.1.4 Infiltration Block (Studies Q8-Q12)

Five infiltration block trials were conducted (four controlled and one uncontrolled) in four different countries abroad. Three of these trials compared 0.75% ropivacaine to 0.25% bupivacaine, one was placebo controlled and the last was ropivacaine treatment alone [Note: no study report was submitted for this study – Study Q8 and no infiltration block indication is being sought).

ASA I-III patients, aged 21-69 years, in a double-blind fashion, received either 40-ml ropivacaine 7.5 mg/ml (300 mg) or 40-ml bupivacaine 2.5 mg/ml (100 mg). These studies compared field block to wound infiltration for pain control following inguinal hernia repair.

A total of two hundred and eighty-two patients (282) were exposed to ropivacaine versus two hundred and eighteen patients exposed to bupivacaine. In the controlled clinical trials, a total dose of 300 mg of ropivacaine administered versus 100 mg of bupivacaine.

Table 99. Description – Infiltration Clinical Trials

STUDY	DRUG/CONCENTRATION (MG/ML)	DOSE (MG)	NUMBER OF PATIENTS	TOTAL PATIENTS
Q8	Ropivacaine 7.5	300	10	21
	Ropivacaine 7.5	375	10	
	Ropivacaine 7.5	450	1	
Q9	Ropivacaine 7.5	300	73	144
	Bupivacaine 2.5	100	71	
Q10	Ropivacaine 7.5	300	76	153
	Bupivacaine 2.5	100	77	
Q11	Ropivacaine 7.5	300	75	145
	Bupivacaine 2.5	100	70	
Q12	Ropivacaine 7.5	300	37	77
	Placebo	0	40	
				Grand Total: Rop. – N=282 Bup. –N=218 Placebo – N=40

8.1.4.1 Serious Adverse Events

Controlled Clinical Trials

Nineteen serious adverse events were reported – ropivacaine 13 and bupivacaine 6. The percentages of patients experiencing serious adverse events was relatively equal among treatment groups (ropivacaine 3.6% versus bupivacaine 2.8%). The numbers of events were scattered broadly among multiple organ classes. (Please note sponsor's Table 1-6 below for details).

Table 100. Distribution of all Serious Adverse Events - Controlled Trials

Organ class	Preferred term	Ropi (n=224)	Bupi (n=218)	Total
Liver	cholecystitis	2		2
	jaundice		1	1
Myocardial	T wave changes	1		1
Respiratory	respiratory infection	1		1
Red blood cell	anaemia B twelve deficiency	1		1
	hyperhaemoglobinaemia	1		1
White blood cells	leukocytosis	3		3
Urinary	urinary retention		1	1
Reprod,. Male	oedema scrotum		1	1
	scrotal disorder	1		1
Gnrl	postoperative complications	3	3	6
Grand Total		13	6	19
No. of patients		8 (3.6%)	6 (2.8)	

[Item 8, Vol. 107, p. 262]

The serious adverse events that are considered to be related to drug administration are depicted in the table below. Ropivacaine 0.75% was associated with unresolved t wave changes (interpreted to mean myocardial ischemia). Notably, despite the slower rate of absorption typical of the infiltration route of administration, the 0.75% ropivacaine concentration was still capable of causing myocardial ischemia.

Table 101. Related Serious Adverse Events - Controlled Trials

Study	Pat No.	Drug	System organ class	Preferred term	Verbatim	Relative time (hour)[1]
SP-ROA-0006	216	Bupi	heart rate	cardiac arrest	asystole x 10 secs.	0

[Item 8, Vol. 107, p. 263]

Case Narrative:

I. A case of suspected post-infusion cardiac ischemia. Patient 716 (Study Q11) is a 54 years old male whose preoperative investigation was significant for non-specific T-wave abnormalities only. Seventy-four minutes after the start of infiltration, the routine postoperative ECG was suspicious for lateral ischemia. The patient was transferred to the coronary care unit; however work-up (cardiac enzymes and ECG) did not confirm ischemia and the patient was observed in the coronary unit. The patients' condition improved, however, he was discontinued from the study due to this serious adverse event.

Based upon the data provided, it is difficult to determine whether the patient did or did not have cardiac toxicity. It is more plausible that the coronary care unit work-up that included negative cardiac enzymes was the more accurate of the two investigations, however.

II. A case of postoperative wound infection. Patient 102 is a 29 year old male who suffered a surgical wound infection 18 days after surgery. The wound culture was positive and the patient was treated successfully. Clearly there is no causal relationship to study drug administration.

Table 102

Serious Adverse Event Listing Infiltration Block (Studies Q9-Q11) Ropivacaine Treatment						
Trial	**Patient**	**Age (years)**	**Sex***	**Dose ** **	**Adverse Event**	**Outcome/ Withdrawal**
Q11	501	58	**M**	**Ropivacaine 0.75% (300 mg)**	Vitamin B12 Deficiency	Missing/Unknown
	510	42			Postoperative Complication	Recovered
	629	42			Postoperative Complication	Recovered
	646	55			Scrotal Disorder	Recovered
	707	68			Respiratory Infection	Recovered
	716	55			ECG Changes	Recovered
Q9	1034	36	**M**	**Ropivacaine 0.75% (300 mg)**	Postoperative Complications	Recovered
	4001	47			Cholecystitis	Missing/Unknown
					Cholecystitis	Recovered
					Hyperhemaglobinemia	Missing/Unknown
					Leukocytosis	Missing/Unknown

*All patients were male
** All patients received the same dose of ropivacaine.

8.1.4.2 Discontinuations Due to an Adverse Event

Waiting for response from sponsor to clear up discrepancy. At most there was one discontinuation due to an adverse event as described in the case narrative see above.

8.1.4.3 Overall Adverse Event Profile

8.1.4.3.1 *Distribution According to Organ System*

The adverse events with the highest overall incidence, in decreasing order of frequency, are postoperative complications, headache, and dizziness. The difference in frequency between treatment groups was negligible. Interestingly, cardiovascular disorders were infrequent in both groups (less than 2%). Overall, the number of unique adverse events was higher in patients exposed to ropivacaine (117) than bupivacaine (114) in the brachial plexus block trials, but the difference was minute.

Distribution of Unique Adverse Events ≥ 5%: Comparative Infiltration Block Trials (based upon Sponsor's Table (Appendix) 2-2, item 8, vol. 107, p. 286)

EVENT	Ropivacaine N=224 n(%)	Bupivacaine N=218 n(%)
CNS and PNS Disorders		
Headache	8(4)	11(5)
Dizziness	6(3)	8(4)
Gastrointestinal Disorders		
Nausea	13(6)	12(6)
Body as a Whole		
Postoperative Complications	12(5)	15(7)
Liver and Biliary System		
SGPT Increased	8(4)	10(5)
Fever	4(2)	1(0.4)

8.1.4.4 OTHER ADVERSE EVENTS

8.1.4.4.1 *Adverse Events by Age*

The ages of the patients in the infiltration block studies were 18-75 years. Patients were not equally distributed between age groups, i.e., ropivacaine <65 (n=179) and >65 (n=45) versus bupivacaine <65 (n=176) and >65 (n=42); therefore any comparative conclusions between older and younger age groups would be difficult.

However, considering that patients > 65 years of age represented one fourth of the total population and the number of adverse events occurring in patients >65 (13) versus < 65 (104) was one ninth of the population, one can conclude that increasing patient age did not result in increasing adverse events.

In fact, there were very few instances where patients >65 experienced an adverse event. The organ system most commonly affected was male reproductive (scrotal edema 2%, orchitis 2% and testis disorder 2%) and liver and biliary system (SGPT increased 7%). No significant difference was seen between treatment groups with respect to age.

8.1.4.4.1 *Adverse Events by Gender*

Over ninety percent of the patients enrolled were males. This is an expected finding in light of the male preponderance for inguinal herniation. Therefore, no comparative claims can be made with respect to gender.

8.1.4.5 Other Safety Findings

8.1.4.5.1 *Clinical Laboratory Evaluations*

Surprisingly, elevated SGPT levels were more common in the infiltration block studies than in all others submitted. The patients in the postoperative pain management studies who had a higher incidence of abdominal cancers, etc., would be the more likely group of patients to exhibit elevated liver enzymes and yet they did not. One would have to assume this is by chance alone.

8.1.4.5.2 *Drug-Drug Interaction*

No data was submitted.

8.1.4.5.3 *Interaction with Antihypertensives*

No data was submitted.

8.1.4.6 Summary of Potential Adverse Events Considered Related to Study Drug

The infiltration block trials provide further evidence to support increased toxicity associated with 0.75% ropivacaine. While these trials are not submitted in support of any indication they add important insight into the potential lethality of the higher concentration of ropivacaine.

9.0 CONCLUSIONS – SAFETY AND EFFICACY

The clinical trials have demonstrated efficacy of ropivacaine for the performance of postoperative pain management, epidural anesthesia for cesarean section, and brachial plexus block.

With respect to the following proposed indications:

1. Increase in the **dosage** of ropivacaine from 5 mg/ml to 7.5 mg/ml used in:
    d) brachial plexus block,
    e) lumbar epidural for cesarean section and,
    f) thoracic epidural
2. Increase in the **duration** of epidural infusion for post-operative pain management from 24 to 72 hours
3. Increase in the lumbar epidural infusion **rate** from 6-10 ml/h to 6-14 ml/h and,
4. Increase in the thoracic epidural infusion **rate** from 4-8 ml/h to 6-14 ml/h.

Based upon a review of the data submitted and the apparent association between serious adverse events and 0.75% ropivacaine exposure, it would be prudent not to approve an increase in the concentration of ropivacaine from 5 mg/ml to 7.5 mg/ml for the proposed use.

All other proposed increases in the duration of and rate of infusion are acceptable, with cautionary language warning of the potential for the increased incidence of adverse events associated with following:

1. high levels of anesthetic block in debilitated patients (preexisting cardiorespiratory disease, and/or ≥ASA III)
2. prolonged continuous infusions, i.e., >70 hours
3. high rates of infusion, i.e., the rapidity of onset of high levels of anesthesia,

and language warning the practitioner of the

1. possibility of post ropivacaine exposure febrile episodes
2. exceeding dose limits during infiltration and brachial plexus block anesthesia, i.e., 300 and 375 mg [40 and 50 ml of 0.75% ropivacaine] infiltration...or 300 mg [40 ml of 0.75% ropivacaine] brachial block."

10.0 RECOMMENDATIONS

The proposed changes in indications should be approved with the above mentioned limitations.

Monica Roberts, M.D._
DACCAD
8/11/99

Bob Rappaport, M.D.
DACCAD
8/11/99

cc: NDA-20-533
HFD-170 File
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Samanta

APPENDICES

Appendix 10. Line Listing – Serious Adverse Events Postoperative Pain

Serious Adverse Event Listing
Postoperative Pain Management
Ropivacaine Treatment

Trial	Patient	Age (years)	Sex (M/F)	Dose[17]	Adverse Event	Outcome/ Withdrawal
I32	7	57	F	Ropivacaine 0.2% (1487 mg)	Elevated Liver Enzymes (SGOT, SGPT, AP)	Still Present
O10	102	69	F	Ropivacaine 0.2% + fentanyl 2 ug/ml (1227 mg)	Ileus	Recovered
	107	49	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1471 mg)	Pseudomembranous Colitis	Recovered
	108	58	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1486 mg)	Ileus	Recovered
	109	57	M	Ropivacaine 2% (2051)	Postoperative Complications	Still Present
	111	74	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1640 mg)	Ileus	Recovered
	112	75	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1368 mg)	Ileus Postoperative Complications Atelectasis Pleural Effusion	Recovered
	115	59	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(1606 mg)	Dysphagia	Recovered
	117	75	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1464 mg)	Ileus Atelectasis Pleural Effusion	Recovered
	124	72	F	Ropivacaine 2% (1546)	Hypotension	Recovered
	128	67	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(1432 mg)	ECG Changes	Recovered
	131	75	F	Ropivacaine 2% (1229)	Intraoperative adverse event, iatrogenic	Still Present
	132	28	M	Ropivacaine 2% (531)	Enlarged Abdomen Abdominal Pain Intra-abdominal Abscess	Recovered
	205	34	M	Ropivacaine 2% (807)	Postoperative Complications	Recovered

[17] Describes the infusion dose only.

Serious Adverse Event Listing (continued)
Postoperative Pain Management
Ropivacaine Treatment

010 cont.

Patient	Age (years)	Sex (M/F)	Dose[5]	Adverse Event	Outcome/ Withdrawal
212	75	F	Ropivacaine 2% (460)	Postoperative Complications	Recovered
301	71	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(1582 mg)	Pleural Effusion	Recovered
302	39	F	Ropivacaine 2% (137)	Ileus	Recovered
304	75	F	Ropivacaine 2% (137)	Intraoperative adverse event, iatrogenic	Recovered
305	56	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(1877 mg)	Cardiac Failure	Recovered
				Convulsions	
				Gastric Ulcer	
				GI Hemorrhage	
				Intra-abdominal Abscess	
				Peritoneal Abscess	
				Tachycardia	
				Supraventricular Tachycardia	
				Ventricular Tachycardia	
				Sepsis	
				Heart Murmur	
309	78	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(724 mg)	GI Hemorrhage	Recovered
311	77	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(646 mg)	Postoperative Complications	Still Present
				Nausea	Recovered
				Vomiting	Recovered
				Dehydration	Recovered
314	70	M	Ropivacaine 0.2% (1261)	Postoperative Complications	Recovered
316	64	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(216.9 mg)	Postoperative Complications	Died
				Hypotension	Died
				Hypotension	Recovered
				Peritonitis	Died
				Increased Nonprotein Nitrogen	Died
				Coagulation Disorder	Died
				Septic Shock	Died
				Dyspnea	Died
				Hypoxia	Died
				Respiratory Insufficiency	Died
				Acute Renal Failure	Died
319	62	F	Ropivacaine 0.2% (1824)	Ovarian Cyst	Recovered
322	68	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(1919 mg)	Abscess	Still Present

[5] Describes the infusion dose only.

Serious Adverse Event Listing (continued)
Postoperative Pain Management
Ropivacaine Treatment

010 cont.

Patient	Age (years)	Sex (M/F)	Dose[5]	Adverse Event	Outcome/ Withdrawal
325	80	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(15059 mg)	Cardiac Failure	Recovered
				Hypokalemia	
				Pleural Effusion	
326	61	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1244 mg)	Ileus	Recovered
				Urethral Disorder	
330	66	M	Ropivacaine 0.2% (830)	Iatrogenic Intraoperative Adverse event	Recovered
335	75	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1803 mg)	Paralytic Ileus	Recovered
401	55	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(1089 mg)	Postoperative Complications	Recovered
				Cystitis	
405	75	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1245 mg)	Asthenia	Recovered
				Intestinal Obstruction	
				Intestinal perforation	
				Lobar Pneumonia	
				Confusion	
406	72	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1392 mg)	Postoperative Complications	Still Present
				Myocardial Infarction	Recovered
				Pulmonary Edema	Recovered
407	52	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1398 mg)	Intra-abdominal Abscess	Still Present
				Rectal Carcinoma	
411	23	M	Ropivacaine 0.2% (1829)	Aggravated Crohn's Disease	Recovered
				Enteritis	Still Present
412	32	Fl	Ropivacaine 0.2% + fentanyl 2 ug/ml(881 mg)	GI Fistula	Still Present
413	49	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(1067 mg)	Fever	Recovered
				Postoperative Complications	
				Intra-abdominal Abscess	
414	74	M	Ropivacaine 0.2% (1626)	Intestinal Obstruction	Recovered
420	49	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(955 mg)	Ileus	Recovered
422	67	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1467 mg)	Urinary Retention	Recovered
427	50	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1015 mg)	Postoperative Complications	Recovered
				Urinary Retention	
501	53	M	Ropivacaine 0.2% (1957)	Myocardial Infarction	Recovered

[5] Describes the infusion dose only.

Serious Adverse Event Listing (continued) Postoperative Pain Management Ropivacaine Treatment						
Trial	**Patient**	**Age (years)**	**Sex (M/F)**	**Dose[5]**	**Adverse Event**	**Outcome/ Withdrawal**
010 cont.	504	77	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(959.6 mg)	Urinary Retention	Recovered
	506	73	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1046.8 mg)	Postoperative Complications Intestinal Perforation Respiratory Insufficiency	Recovered
	511	51	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(1541 mg)	Intestinal Obstruction Nausea Vomiting	Recovered
	514	47	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(1306.6 mg)	Postoperative Complications Intra-abdominal Abscess	Recovered
	522	48	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(1554 mg)	Vomiting Nausea	Recovered
	530	69	F	Ropivacaine 0.2% (1728 mg)	Paresthesia Speech Disorder Abnormal Coordination	Still Present
	603	51	M	Ropivacaine 0.2% (1495.3 mg)	GI Neoplasm, malignant	Died
	604	50	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(1003.3 mg)	Flatulence Nausea Vomiting Enlarged Abdomen	Recovered
	606	70	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1211.9 mg)	Duodenal Ulcer GI Fistula Carcinoma Intestinal Obstruction	Recovered
	611			Ropivacaine 0.2% (1228 mg)	Postoperative Complication Carcinoma	Still Present
	613	66	M	Ropivacaine 0.2% (106.5 mg)	Postoperative Complication	Recovered
	614	71	F	Ropivacaine 0.2% (1429 mg)	Intestinal Obstruction	Recovered

[5] Describes the infusion dose only.

Serious Adverse Event Listing (continued)
Postoperative Pain Management
Ropivacaine Treatment

Trial	Patient	Age (years)	Sex (M/F)	Dose[5]	Adverse Event	Outcome/ Withdrawal
011	107	62	M	Ropivacaine 0.2% (1817 mg)	Postoperative Complication	Recovered
	113	76	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1542 mg)	Sepsis	
	120	70	M	Ropivacaine 0.2% + fentanyl 4 ug/ml(665.3 mg)	Coma	Recovered
					Respiratory Depression	
	203	61	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1542 mg)	Abdominal Pain	Recovered
	204	66	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1213 mg)	Abdominal Pain	Recovered
					Nausea	
	205	66	M	Ropivacaine 0.2% + fentanyl 1 ug/ml(1471 mg)	Abdomen Enlarged	Still Present
	214	48	M	Ropivacaine 0.2% + fentanyl 1 ug/ml(700 mg)	Ascites	Still Present
	218	68	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(407.3 mg)	Micturition Disorder	Recovered
	303	71	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(513.2mg)	Arrhythmia	Recovered
	312	48	M	Ropivacaine 0.2% + fentanyl 1 ug/ml(1751 mg)	Thrombosed Hemorrhoids	Recovered
	316	68	M	Ropivacaine 0.2% + fentanyl 1 ug/ml(271 mg)	Pulmonary Edema	Recovered
	317	61	F	Ropivacaine 0.2% (565 mg)	Postoperative Complication	Recovered
	321	67	M	Ropivacaine 0.2% + fentanyl 4 ug/ml(1678 mg)	Hypertension	Recovered
					Encephalopathy	
					Tachycardia	
	324	78	M	Ropivacaine 0.2% + fentanyl 4 ug/ml(1119 mg)	Left Cardiac failure	Still Present
					Stupor	Recovered
					Hypoproteinemia	Still Present
					Muscle Weakness	Recovered
					Hypoxia	Still Present
					Pulmonary Edema	Died
					Respiratory Disorder	Recovered
					Respiratory Insufficiency	Recovered
					Oliguria	Still Present
	404	73	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1138 mg)	Jaundice	Recovered
	406	50	F	Ropivacaine 0.2% + fentanyl 4 ug/ml(1306 mg)	Unexpected Therapeutic Effect	Recovered

[5] Describes the infusion dose only.

Serious Adverse Event Listing (continued) Postoperative Pain Management Ropivacaine Treatment						
Trial	**Patient**	**Age (years)**	**Sex (M/F)**	**Dose[5]**	**Adverse Event**	**Outcome/ Withdrawal**
011 cont.	407	73	M	Ropivacaine 0.2% + fentanyl 4 ug/ml(1382 mg)	Postoperative Complication	Still Present
					Hypotension	Recovered
					Hematemesis	Recovered
					Anemia	Recovered
	409	60	M	Ropivacaine 0.2% (235 mg)	Fever	Recovered
	410	55	M	Ropivacaine 0.2% + fentanyl 4 ug/ml(522.1 mg)	Diarrhea	Recovered
	412	60	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1473mg)	Postoperative Complication	Recovered
	414	66	M	Ropivacaine 0.2% + fentanyl 1 ug/ml(1089.7 mg)	Intestinal Obstruction	Recovered
	417	31	M	Ropivacaine 0.2% + fentanyl 4 ug/ml(522.1 mg)	Sepsis	Recovered
					Respiratory Insufficiency	
	422	43	M	Ropivacaine 0.2% + fentanyl 1 ug/ml(720 mg)	Intestinal Obstruction	Still Present
					Intestinal Obstruction	
	506	52	F	Ropivacaine 0.2% (155 mg)	Pneumonia	Recovered
	606	57	F	Ropivacaine 0.2% + fentanyl 4 ug/ml(1273 mg)	Postoperative Complication	Recovered
	608	70	M	Ropivacaine 0.2% (1566 mg)	Postoperative Complication	Still Present
	610	56	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1374.2 mg)	Infection	Still Present
	616	51	F	Ropivacaine 0.2% + fentanyl 1 ug/ml(1130.6 mg)	Cardiac Arrest	Died
	617	27	F	Ropivacaine 0.2% + fentanyl 4 ug/ml(155 mg)	Hemorrhage	Recovered
	702	63	M	Ropivacaine 0.2% + fentanyl 1 ug/ml(828.6 mg)	Postoperative Complication	Still Present
					Deep Venous Thrombosis	
	704	70	M	Ropivacaine 0.2% + fentanyl 4 ug/ml(235 mg)	Respiratory Insufficiency	Recovered

[5] Describes the infusion dose only.

Serious Adverse Event Listing (continued) Postoperative Pain Management Ropivacaine Treatment						
Trial	**Patient**	**Age (years)**	**Sex (M/F)**	**Dose[5]**	**Adverse Event**	**Outcome/ Withdrawal**
011 cont.	712	27	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1988.9 mg)	Postoperative Complication	Recovered
					Postoperative Complication	Still Present
	714	59	F	Ropivacaine 0.2% (1963 mg)	Ovarian Carcinoma	Died
	717	66	M	Ropivacaine 0.2% + fentanyl 41 ug/ml(1860 mg)	Fever	Recovered
	728	75	F	Ropivacaine 0.2% (1968 mg)	Cardiovascular Disorder	Recovered
					Pulmonary Embolism	
					Pneumonia	
	803	52	F	Ropivacaine 0.2% + fentanyl 1 ug/ml(1509.2 mg)	Unexpected Therapeutic Effect	Recovered
	808	35	F	Ropivacaine 0.2% + fentanyl 4 ug/ml(1361 mg)	Intra-abdominal Abscess	Recovered
	815	68	?	Ropivacaine (2043 mg)	Postoperative Complication	Recovered
	906	76	M	Ropivacaine 0.2% + fentanyl 4 ug/ml(1702 mg)	Hypotension	Recovered
					Sick Sinus Syndrome	Recovered
	912	65	M	Ropivacaine 0.2% + fentanyl 4 ug/ml(1604 mg)	Postoperative Complication	Recovered
	916	58	F	Ropivacaine 0.2% + fentanyl 1 ug/ml(2056 mg)	Postoperative Complication	Still Present
	918	77	M	Ropivacaine 0.2% + fentanyl 1 ug/ml(727 mg)	Myocardial Infarction	Died
	1001	56	F	Ropivacaine 0.2% + fentanyl 4 ug/ml(1359.5 mg)	Infection	Recovered
	1003	68	M	Ropivacaine 0.2% + fentanyl 1 ug/ml(82.5 mg)	Thrombocytopenia	Still Present
	1004	64	F	Ropivacaine 0.2% + fentanyl 4 ug/ml(1652 mg)	Postoperative Complication	Recovered
					Atrial Flutter	Recovered

[5] Describes the infusion dose only.

Serious Adverse Event Listing (continued) Postoperative Pain Management Ropivacaine Treatment						
Trial	**Patient**	**Age (years)**	**Sex (M/F)**	**Dose[5]**	**Adverse Event**	**Outcome/ Withdrawal**
011 cont.	1008	33	M	Ropivacaine 0.2% (1098 mg)	Bowel Irregularity	Recovered
	1009	61	M	Ropivacaine 0.2% + fentanyl 2 ug/ml(1078.7 mg)	Esophagitis	Recovered
	1010	52	F	Ropivacaine 0.2% + fentanyl 1 ug/ml(1474.4 mg)	Dyspepsia	Still Present
					Infection	Still Present
	1012	40	M	Ropivacaine 0.2% + fentanyl 4 ug/ml(754 mg)	Infection	Still Present
	1104	73	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(1535.2 mg)	Infection	Recovered
	1122	75	M	Ropivacaine 0. 2% (1673 mg)	Death	Died
					Postoperative Complication	Recovered
	1203	68	F	Ropivacaine 0.2% (434 mg)	Pulmonary Embolism	Still Present
	1207	75	F	Ropivacaine 0.2% + fentanyl 2 ug/ml(1023 mg)	Pulmonary Embolism	Recovered
013	104	78	F	Ropivacaine 0.2% (1673 mg)	Constipation	Recovered
					Nausea	
					Vomiting	
015	7	62	M	Ropivacaine 1% (332 mg)	Fracture	Improved
	90	56	M	Ropivacaine 1% (670 mg)	Postoperative Complication	Recovered
	95	32	F	Ropivacaine 1% (616 mg)	Paresis	Recovered
	100	46	M	Ropivacaine 1% (568 mg)	Urinary Retention	Recovered
09	1	74	F	Ropivacaine 1% (1051 mg)	Hydronephrosis	Still Present
					Deep Venous Thrombosis	
	9	74	M	Ropivacaine 1% (1270 mg)	Postoperative Complication	Improved
					Postoperative Complication	Recovered

[5] Describes the infusion dose only.

NDA: #20-533 **Serial #:** S-002

NAME: Naropin (ropivacaine HCl injection)

SPONSOR: AstraZeneca

REVIEW DATE: 09-30-99

TYPE OF REVIEW: Submission in response to an "Approvable" action

REVIEWER: Patricia Hartwell, MD MBA

CONDITIONS FOR APPROVAL (Ref. Approvable Letter 9-28-99):

Submission of all safety information regarding the new drug covering all studies and uses of the drug:

- Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission
- Retabulation of drop-outs with new drop-outs identified
- Details of any significant changes or findings
- Summary of worldwide experience on the safety of this drug
- Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event
- English translations of any approved foreign labeling not previously submitted
- Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events

NEW STUDIES INCLUDED IN THIS SUBMISSION:

- CF-ROP-0002: "Femoral nerve block for postoperative pain relief after major knee surgery. A double blind comparison of ropivacaine 7.5 mg/mL and placebo."
- 92Ro64: "A double blind comparison between epidural ropivacaine 0.25% and bupivacaine 0.25% given as top-up doses for pain relief during labour"
- 94Ro79: "Continuous epidural infusion of ropivacaine 2 mg/mL for pain relief during labour: A volume response study"
- 95Ro87: "An open randomized study of ropivacaine 2 mg/mL administered as continuous epidural infusion in four different infusion rates for the relief of childbirth pain"

This review will sequentially address the above approvable issues. Only updated safety information will be included in the present review. New efficacy data will require a separate submission and will be provided by the sponsor at a future date.

RETABULATION OF ALL SAFETY DATA

Adverse events with incidence of ≥1% - adults receiving regional or local anesthesia

Surgery, Labor, Caesarian Section, Post-operative Pain, Peripheral Nerve Block, Local Infiltration Total # (percentage)				
Preferred Term	**Previous Data**		**Updated Data**	
	Ropivacaine (N=742)	*Bupivacaine (N=737)*	*Ropivacaine (N=1661)*	*Bupivacaine (N=1433)*
Hypotension	237 (31.9)	225 (30.5)	536 (32.3)	408 (28.5)
Nausea	92 (12.4)	96 (13)	283 (17)	207 (14.4)
Paresthesia	51 (6.9)	44 (6)	82 (4.9)	57 (4)
Vomiting	48 (6.5)	38 (5.2)	117 (7)	88 (6.1)
Back Pain	36 (4.9)	47 (6.4)	73 (4.4)	75 (5.2)
Pain	39 (5.3)	40 (5.4)	71 (4.3)	71 (5)
Bradycardia	32 (4.3)	38 (5.2)	96 (5.8)	88 (6.1)
Headache	23 (3.1)	26 (3.5)	84 (5.1)	68 (4.7)
Fever	25 (3.4)	20 (2.7)	61 (3.7)	37 (2.6)
Chills	16 (2.2)	14 (1.9)	42 (2.5)	24 (1.7)
Dizziness	18 (2.4)	10 (1.4)	42 (2.5)	23 (1.6)
Pruritus	16 (2.2)	11 (1.5)	63 (3.8)	40 (2.8)
Urinary retention	10 (1.3)	12 (1.6)	23 (1.4)	20 (1.4)
Hypoesthesia	8 (1.1)	10 (1.4)	27 (1.6)	24 (1.7)
Postop complications			41 (2.5)	44 (3.1)
Labor progress poor			23 (1.4)	22 (1.5)
Anxiety			21 (1.3)	11 (0.8)
Breast feeding poor			21 (1.3)	12 (0.8)
Rhinitis			18 (1.1)	13 (0.9)

The incidence of adverse events in the combined data was generally consistent with that reported in the previous data. The comparative incidences between ropivacaine and bupivacaine in the combined data were also consistent with those in the previous data.

Adverse events with incidence ≥1% - neonates of patients in controlled clinical trials

Caesarian Section and Labor Analgesia Trials Total # (percentage)				
Preferred Term	**Previous Data**		**Updated Data**	
	Ropivacaine (N=337)	*Bupivacaine (N=317)*	*Ropivacaine (N=639)*	*Bupivacaine (N=573)*
Fetal bradycardia	58 (17.2)	53 (16.7)	77 (12.1)	68 (11.9)
Neonatal jaundice	12 (3.6)	12 (3.8)	49 (7.7)	47 (8.2)
Neonatal tachypnea	8 (2.4)	11 (3.5)	14 (2.2)	15 (2.6)
Fetal tachycardia	7 (2.1)	8 (2.5)	13 (2)	12 (2.1)
Neonatal fever	6 (1.8)	8 (2.5)	13 (2)	14 (2.4)
Fetal distress	4 (1.2)	8 (2.5)	11 (1.7)	10 (1.7)
Neonatal resp distress	5 (1.5)	4 (1.3)	17 (2.7)	18 (3.1)
Neonatal vomiting	5 (1.5)	1 (0.3)	5 (1.0)	1 (0.1)
Neonatal complic NOS			42 (6.6)	38 (6.6)
Low Apgar score			18 (2.8)	14 (2.4)
Neonatal infection			10 (1.6)	8 (1.4)
Neonatal hypoglycemia			8 (1.3)	16 (2.8)

With the exception of "neonatal jaundice" the incidence of adverse events in the combined data was equal to or less than that reported in the previous data. Also, consistent with previous data, the incidence of adverse events in the ropivacaine group was generally less than that in the bupivacaine group.

RETABULATION OF DROP-OUTS WITH NEW DROP-OUTS IDENTIFIED

No patient drop-outs occurred in the new studies and therefore no retabulation was submitted.

DETAILS OF ANY SIGNIFICANT CHANGES OR FINDINGS

Upon comparison of the previously submitted data with the compilation of old data and with the results from the four additional studies, this reviewer identified no significant changes or findings.

SUMMARY OF WORLDWIDE SAFETY EXPERIENCE (9-95 through 9-99)

The following four issues of special interest have been previously identified and updated information is contained in this submission.

Temperature Elevation

The incidence of temperature elevation has remained constant throughout the reporting period and was more commonly observed in the post-operative setting.

Poor/Failed Progression of Labor

The incidence of poor or failed progression of labor attributed to the use of ropivacaine was approximately 10% in 1996 and 1997 (information obtained from a general questionnaire given to physicians to report all serious adverse events). This incidence also corresponds to the commonly accepted frequency of unplanned Caesarian Section in the United States (10-15%), thus calling into question a cause/effect relationship with ropivacaine use. Subsequently, reports of these events have declined to insignificant numbers.

Fetal and Neonatal Events

During 1996 and 1997 a general questionnaire was distributed to obstetricians and other physicians performing deliveries. This questionnaire was designed to elicit reports of fetal and neonatal bradycardia, fetal death, fetal distress, low Apgar scores, and poor progression of labor. As expected, the total number of reports was dramatically increased but the incidence of these adverse events was in keeping with those previously reported. Subsequently, no clinically significant differences between ropivacaine and bupivacaine with regard to neonatal outcome or incidence of adverse events have been seen.

Convulsions, Suspected Toxic Events, and Cardiovascular Events

The number of reports for both neurotoxic and cardiotoxic events has increased during the reporting period. However, this increase parallels the increase in patient exposure during the same time period and the resultant incidences have remained constant. Toxic reactions continue to be rarely encountered (neurotoxicity - 12 per million patients, cardiotoxicity - 6.3 per million patients).

CASE REPORT FORMS FOR DEATHS AND WITHDRAWALS DUE TO AE's

No deaths or withdrawals because of an adverse event occurred in the additional studies. Therefore, no case report forms were submitted or evaluated.

ENGLISH TRANSLATIONS OF NEW FOREIGN LABELING

Translation of the labeling approved on June 16, 1999 for use in the following countries was submitted.

- Holland, Austria, Belgium, Luxembourg, Denmark, France, Germany, Greece, Italy, Portugal, Spain, UK/Ireland, Finland, Iceland, Switzerland, Czech Republic

New Zealand labeling, approved on February 2, 1999 and Swedish labeling, approved on February 11, 2000 have also been provided.

INFORMATION SUGGESTING A SUBSTANTIAL DIFFERENCE IN OCCURRENCE OF COMMON AE's

After examination of all data contained in this submission, this reviewer has determined that there is no substantial difference in the occurrence of common adverse events than was reported in the foregoing submission.

LABELING REVIEW

Following is a listing and analysis of relevant differences between the agency's draft labeling on the "approvable" action (9-28-99) and the sponsor's version of an updated label for this submission (5-1-00). The labeling comparisons relevant to safety information have been evaluated. Efficacy information will be re-submitted at a later date.

CLINICAL TRIALS

[redacted] should be removed.
The standard for presentation of clinical information is to be based on the ITT population.

Epidural Administration in Surgery

[redacted]

submitted in the original 1996 NDA application and does not include any new information. Therefore, language should revert back to the 1996 Approval letter.

Epidural Administration in Cesarean Section
Sponsor has removed a table summarizing new studies from 1999 submission and converted the information into prose. This is acceptable with minor revisions. The total

[redacted] An explanatory footnote to the deleted table should be added to the end of the descriptive section – *"Some patients received other anesthetic, analgesic, or sedative modalities during the course of the operative procedure."* Without this phrase, the paragraph misrepresents the activity of the studied agent.

Epidural Administration in Labor and Delivery
Sponsor's phrase *"9 double-blind clinical studies involving 240* [redacted] *patients"* is accurate and acceptable. The language of the approved 1996 label was inaccurate because of the inadvertent addition of an open-label trial.

Epidural Administration in Postoperative Pain Management
The language of the first two paragraphs has been altered by the sponsor and should be changed back to that contained in the 1999 Approvable letter. In some cases, the

sponsor's language misrepresents the actual findings of the supportive studies. Review of the 1999 submission and reviews do not support the altered language.

At the end of the 4th paragraph the sponsor has added the statement [redacted] This statement is a supposition and the submitted trials were not designed to address or evaluate this parameter.

Peripheral Nerve Block

In the 1st paragraph, sponsor has changed the phrase "Naropin 5.0 mg/ml, in doses up to 275 mg" to read [redacted]. Because the 1996 accepted language was "5.0 mg/ml and the new studies of the 1999 submission did not use a concentration of 2.5 mg/ml, this change is not acceptable.

Local Infiltration

The sponsor has added the language [redacted] to the approvable label. Even though the sponsor reported additional local infiltration studies in the 1999 submission, they did not want them included in the efficacy trials. Therefore, the language should revert to the 1996 approved language and this phrase should be deleted.

WARNINGS

The sponsor has altered the 1st paragraph to read "...may result in *cardiac arrhythmia* or cardiac arrest. The potential for successful resuscitation has not been studied *in humans.* [redacted]

The addition of "cardiac arrhythmia" is clinically correct and is acceptable. The phrase [redacted] should be deleted as this implies that previous studies have shown successful resuscitation in other species. Sponsor proposes the addition of "[redacted] This phrase should be deleted as it incorrectly implies that only amide local anesthetics are capable of causing toxic reactions.

PRECAUTIONS

General: Sponsor has added the phrase [redacted] 1. This change does not reflect data from either the original 1996 application or the 1999 supplement. The original language from the 1996 Accepted action, "may result in cardiovascular depression" should be restored.

Ophthalmic Surgery: Sponsor has deleted the phrase *"Until appropriate experience is gained, the use of Naropin for ophthalmic surgery is not recommended."* No new data was presented in the 1999 submission in support of this deletion. Therefore, this statement, contained in the original Accepted label should be restored.

ADVERSE REACTIONS

The sponsor has updated patient numbers and percentages of specific events with data from the 1999 supplement. Review of the supplement and the corresponding review confirmed this update and the changes are acceptable.

Neurologic Reactions
Sponsor has divided this section into [redacted] and [redacted]. This change is confusing and the language should revert to that from the Approvable label.

In both the 1996 and the 1999 draft versions, the statement "In a survey of studies of epidural anesthesia, overt toxicity progressing to convulsions occurred in approximately 0.1% of local anesthetic administrations" was made. In the new label, the sponsor has changed this to "[redacted]". No new information has been provided for this change and the statement should revert back to its original Accepted form.

OVERDOSAGE

Sponsor has added the phrase "...related to high plasma levels *encountered, or large doses administered,* during therapeutic..." This change is acceptable as it accurately reflects the clinical situation.

Management of Local Anesthetic Emergencies:
Sponsor has added "[redacted]" to the title of this section. This statement is inaccurate and should be deleted. Local anesthetic emergencies constitute a variety of events and are not all the result of overdose. In the text of this section, the word [redacted] is used several times. This is actually a misrepresentation (as explained above) and should be changed to the term "toxicity"

DOSAGE AND ADMINISTRATION

The language *"initial epidural block with* [redacted] is not accurate. This would denote the use of [redacted] Naropin. The appropriate language is "5-7 mL".

CONCLUSION

The additional safety data provided by the sponsor is similar to that contained in the "approvable" submission. No new concerns or adverse events have been identified.

/S/

Patricia Hartwell, MD MBA
Medical Officer

/S/

Bob A. Rappaport
Deputy Division Director

CC: Division File
Original NDA #20-533
HFD-170 – McCormick, Rappaport, Hartwell, Compton

NDA: #20-533

NAME: Naropin (Ropivacaine HCL Injection)

SPONSOR: Astra, USA

REVIEW DATE: 09/20/99

TYPE OF REVIEW: Addendum to NDA

REVIEWER: Patricia Hartwell, MD MBA

ADDENDUM TO MEDICAL OFFICER REVIEW:

Information Inadvertently Omitted from Original Review:

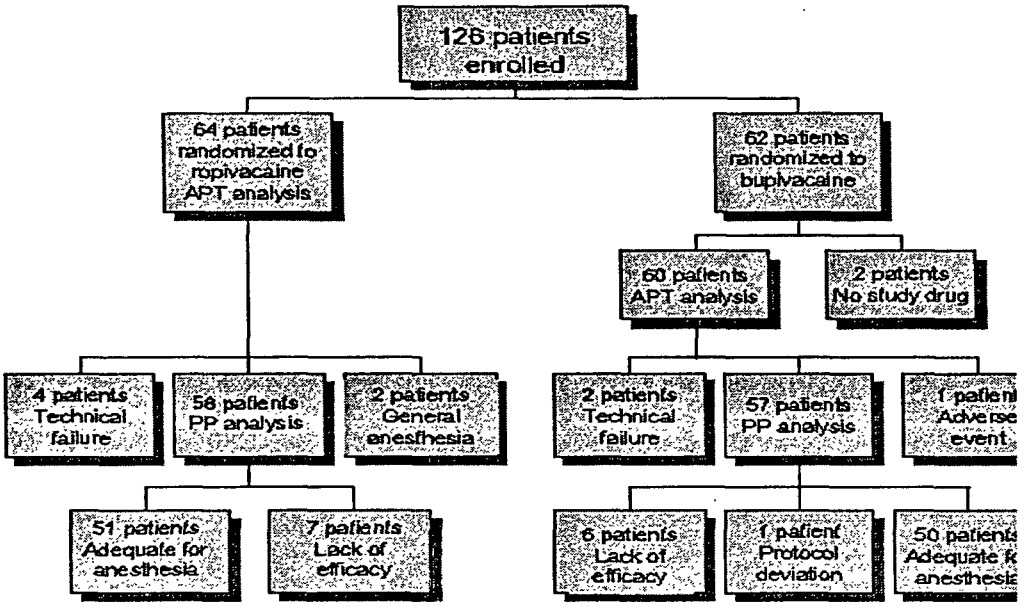
SECTION 7.2.5 STUDY 95RO89 (M09)

Section 7.2.5.4 **Conduct of Study**

Patient Distribution/Disposition:

Of the 126 patients enrolled in the study, all were randomized to receive either ropivacaine 7.5 mg/mL (64) or bupivacaine 5 mg/mL (62). Two patients in the bupivacaine group were withdrawn from efficacy analysis due to technical failures prior to receiving any study drug, leaving 124 total patients (64 ropivacaine and 60 bupivacaine) in the APT group utilized for safety analysis. 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 withdrawn from the APT groups, leaving 58 ropivacaine patients and 57 bupivacaine patients in the PP group used for efficacy analysis. Patient disposition for each treatment group is graphically represented in the following diagram.

Figure 2. Patient Disposition



[Based on Sponsor's diagram Item 8, Vol. 82, p. 45]

Thirteen patients in each treatment group were prematurely discontinued from the study. The following table delineates assigned group and individual reason for discontinuation.

Table 1 Premature Discontinuation

Reason for Discontinuation	*Patient #*	*Ropivacaine 7.5 mg/mL*	*Bupivacaine 5 mg/mL*	*Included in Efficacy Studies*
Technical Failure – after drug	0105, 0113, 0201, 0221	X (4)		NO
Technical Failure – before drug	0219, 0261		X (2)	NO
Technical Failure – after drug	0210, 0233		X (2)	NO
Adverse Event	0021, 0219		X (2)	NO
Lack of Efficacy – General anesth	0012, 0020	X (2)		*PARTIALLY
Lack of Efficacy – Spinal anesth	0034, 0215, 0224, 0231, 0232, 0249	X (6)		*PARTIALLY
Lack of Efficacy – Analgesics	0309	X (1)		*PARTIALLY
Lack of Efficacy – General anesth	0009		X (1)	*PARTIALLY
Lack of Efficacy – Spinal anesth	0239		X (1)	*PARTIALLY
Lack of Efficacy – Analgesics	0002, 0209, 0306, 0308		X (4)	*PARTIALLY
Protocol Violation – Other analgesics	0033		X (1)	*PARTIALLY

* Efficacy measurements included up to time of additional analgesia/anesthesia
[Item 8, Vol. 82, pp. 50-52]

/S/

Patricia Hartwell, MD MBA
Medical Officer

/S/

CC: