Demographics

The following table summarizes the demographic characteristics of the two treatment groups:

Table 191. Demographics - Intent-to-Treat Population

Table 2 Patient Demographics and Baseline Characteristics: Intent-to-Treat Population

Variable	Levobupivacaine N=20	No Block N=15
Sex N (%)		
Male	17 (85.0)	14 (93.3)
Female	3 (15.0)	1 (6.7)
Race N (%)		
Caucasian	17 (85.0)	14 (93.3)
Black	3 (15.0)	0
Asian	0	0
Hispanic	0	0
Other	0	1 (6.7)
Age (years)		
Mean (S.D.)	5.67 (3.91)	6.21 (2.88)
Median	5.35	6.10
Minimum	0.6	0.5
Maximum	12.5	12.2
Height (cm)		
N	17	14
Mean (S.D.)	109.82 (27.40)	115.96 (21.26)
Median	112.00	116.50
Minimum	68.8	66.3
Maximum	157.5	150.0
Weight (kg)		
Mean (S.D.)	23.01 (13.36)	24.15 (9.55)
Median	20.25	23.00
Minimum	7.8	8.1
Maximum	53.6	50.8

Abstracted from Statistical Table 3.1

[Sponsor's Table 2, Item 8, Vol.1.92, p. 037]

"Thirty-one (88.6%) of the patients were male and four (11.4%) were female. Patients ranged in age from 6 months to 12.5 years with a mean of 5.9 years. The majority of patients (31/35, 88.6%) were Caucasian, 3 of 35 (8.6%) were black, and one (2.9%) was in the category "Other".

"The mean height was 112.59 cm (range 66.3 to 157.5 cm). The mean weight was 23.5 kg (range 7.8 to 53.6 kg)."

"Physical examinations showed normal findings for the majority of patients in both groups. Three patients in the 0.5% levobupivacaine group had one or more abnormalities detected on examination involving the body systems of head, neck, and thyroid, ears, nose and throat, and the lungs. One patient had an abnormality in the body system of head neck, and thyroid."

"Concomitant medications most frequently administered in this study included pre-operative sedative agents, prophylactic agents for nausea, anesthetics, anesthetic reversing agents, and pain medication."

[Item 8, Vol. 1.92, p.037]

SPONSOR'S EFFICACY RESULTS:

Primary Efficacy Variable

"The primary efficacy parameter in this study was the proportion of patients needing rescue analgesia in the two-hour post-operative period. Forty-five percent of patients in the 0.5% levobupivacaine group compared with 73.3% of patients in the no block required at least one dose of rescue analgesia (p=0.167). The majority of the children who required rescue (91.4%) required two or fewer doses of rescue analgesia."

Similar results were found upon analysis of the per-protocol population.

[Item 8, Vol. 1.92, p. 038]

Table 192. Proportion of Patients Requiring Rescue Analgesia: Intent-to-Treat Population

Table 3 Proportion of Patients Requiring Rescue Analgesia: Intent-to-Treat Population

	0.5% Levobupivacaine			No Block		
Patients	Unilateral N=15	Bilateral N=5	Overall N=20	Unilateral N=12	Bilateral N=3	Overall N=15
Received at least one rescue medication N (%)	6 (40)	3 (60)	9 (45)*	9 (75)	2 (66.7)	11 (73.3)*
Received no rescue medication N (%)	9 (60)	2 (40)	11 (55)	3 (25)	1 (33.3)	4 (26.7)
Received one dose	2 (33.3)	3 (100)	5 (55.6)	4 (44.4)	0	4 (36.4)
Received two doses	3 (50)	0	3 (33.3)	3 (33.3)	2 (100)	5 (45.5)
Received three doses	1 (16.7)	0	1 (11.1)	1 (11.1)	0	1 (9.1)
Received three or more doses	0	0	0	1 (11.1)	0	1 (9.1)

Abstracted from Statistical Table 6.1

* p=0.167, proportional difference (95% C.I.) -0.283 (-0.623, 0.623)

[Sponsor's Table 3, Item 8, Vol. 1.92, p. 039]

Table 193. Proportion of Patients Requiring Rescue Analgesia:
Per-Protocol Population

Table 4 **Proportion of Patients Requiring Rescue Analgesia: Per-Protocol Population**

	0.5% Levobupivacaine			No Block		
Patients	Unilateral N=15	Bilateral N=5	Overall N=20	Unilateral N=12	Bilateral N=1	Overall N=13
Received at least one rescue medication N (%)	6 (40)	3 (60)	9 (45)*	9 (75)	1 (100)	10 (76.9)*
Received no rescue medication N (%)	9 (60)	2 (40)	11 (55)	3 (25)	0	3 (23.1)
Received one dose	2 (33.3)	3 (100)	5 (55.6)	4 (44.4)	0	4 (40)
Received two doses	3 (50)	0	3 (33.3)	3 (33.3)	1 (100)	4 (40)
Received three doses	1 (16.7)	0	1 (11.1)	1 (11.1)	0	1 (10)
Received three or more doses	0	0	0	1 (11.1)	0	1 (10)

Abstracted from Statistical Table 6.2
* p=0.087, proportional difference (95% C.I.) –0.319 (-0.038, 0.683)

[Sponsor's Table 4. Item 8, Vol. 1.92, p. 039]

Secondary Efficacy Variables

The secondary efficacy parameters in this study were to compare the two treatment groups on the degree of pain expressed, using the CHEOPS scale, the time to first request for rescue medication, the volume of rescue medication, and an overall assessment of the block."

"CHEOPS scores were analyzed in four ways:

- The mean change from Baseline ignoring the use of rescue medication
- CHEOPS scores at or prior to rescue carried forward
- CHEOPS AUCMB until the time of rescue
- CHEOPS AUCMB to the end of the two hour study period"

"The mean increase in the CHEOPS pain scores from Baseline ignoring the use of rescue analgesia were significantly higher ($p-< 0.05$) in the no block group over the 0.5% levobupivacaine group at the time points of 15, 25, and 30 minutes following Time 0."

The CHEOPS scores for the 0.5% levobupivacaine and no block groups as the last CHEOPS score at or before the administration of rescue medication carried forward showed that statistically significant differences occurred at the following time points: 15, 25, 30, 45, 60, 90, and 120 minutes following Time 0, "...indicating that on average, patients in the 0.5% levobupivacaine treatment were experiencing less post-operative discomfort as measured by the CHEOPS scale."

"CHEOPS scores analyzed by the area under the curve minus Baseline (AUCMB) to the time of administration of rescue medication was statistically significant ($p=0.013$) with a mean difference of 4.7 and 95% confidence interval (-1.2, -0.2). CHEOPS scores analyzed by AUCMB to the end of the two-hour study period were also ınificant ($p=0.030$) with a mean difference of -0.5 and 95% confidence interval (-1.0, -0.1). These two analyses dicate that on average, patients in the 0.5% levobupivacaine group experienced less pain than patients who received no block."

Table 194. Analysis of Secondary Efficacy Variable

Table 5 CHEOPS Scores At or Before Administration of Rescue Medication: Intent-to-Treat Population

Time Point	0.5% Levobupivacaine	No Block	Mean Difference (95% C.I.)	p-value
5 minutes				
N	15	10	0 (NE, NE)	NE
Mean (SD)	0	0		
Median	0	0		
Minimum	0	0		
Maximum	0	0		
10 minutes				
N	20	14	-0.3 (-1.1, 0.5)	0.445
Mean (SD)	0.4 (0.88)	0.6 (1.34)		
Median	0	0		
Minimum	0	0		
Maximum	3	4		
15 minutes				
N	20	14	-1.0 (-1.9, 0.0)	0.042
Mean (SD)	0.3 (0.92)	1.3 (1.77)		

Time Point	0.5% Levobupivacaine	No Block	Mean Difference (95% C.I.)	p-value
Median	0	0		
Minimum	0	0		
Maximum	3	5		
20 minutes				
N	20	15	-0.9 (-2.0, 0.3)	0.131
Mean (SD)	0.8 (1.48)	1.6 (1.76)		
Median	0	1.0		
Minimum	0	0		
Maximum	5	5		
25 minutes				
N	20	15	-1.5 (-2.8, -0.1)	0.031
Mean (SD)	1.0 (1.59)	2.5 (2.26)		
Median	0	2.0		
Minimum	0	0		
Maximum	5	5		
30 minutes				
N	20	15	-1.8 (-3.1, -0.6)	0.006
Mean (SD)	1.1 (1.65)	2.9 (2.02)		
Median	0	4.0		
Minimum	0	0		
Maximum	5	5		
45 minutes				
N	20	15	-1.9 (-3.4, -0.4)	0.016
Mean (SD)	1.6 (2.19)	3.5 (2.10)		
Median	0	4.0		
Minimum	-1	0		
Maximum	5	6		
1 hour				
N	20	15	-1.9 (-3.5, -0.3)	0.024
Mean (SD)	1.6 (2.46)	3.5 (2.10)		
Median	1.0	4.0		
Minimum	-2	0		
Maximum	5	6		
1 hour 15 min				
N	20	15	-1.0 (-2.5, 0.6)	0.215
Mean (SD)	2.3 (2.03)	3.3 (2.49)		
Median	2.5	4.0		
Minimum	-1	-2		
Maximum	5	6		
1 hour 30 min				
N	20	15	-1.6 (-3.2, 0.0)	0.050
Mean (SD)	1.8 (2.38)	3.4 (2.20)		
Median	1.0	4.0		
Minimum	-2	0		
Maximum	5	6		
1 hour 45 min				
N	20	15	-1.6 (-3.3, 0.1)	0.063
Mean (SD)	1.8 (2.53)	3.4 (2.29)		
Median	2.0	4.0		
Minimum	-2	-1		
Maximum	5	6		
2 hours				
N	20	15	-1.9 (-3.5, -0.2)	0.027
Mean (SD)	1.7 (2.60)	3.5 (2.03)		
Median	1.5	4.0		
Minimum	-2	0		
Maximum	5	6		

Abstracted from Statistical Table 7.2

[Sponsor's Table 5, Item 8, Vol. 1.92, p. 040-041]

Table 195. CHEOPS Area Under the Curve Minus Baseline (AUCMB) to the Time of Rescue Medication

TABLE 7.3

CHEOPS AUCMB TO RESCUE

INTENT-TO-TREAT PATIENTS

VARIABLE	0.5% LEVOBUPIVACAINE			NO BLOCK			MEAN DIFFERENCE (95% CI) (1)	P-VALUE (2)
	UNILATERAL	BILATERAL	OVERALL	UNILATERAL	BILATERAL	OVERALL		
N	15	5	20	12	3	15	-0.7	0.013
MEAN	0.4430	0.8178	0.5367	1.3313	0.7797	1.2210	(-1.2, -0.2)	
MEDIAN	0.3750	1.0000	0.4790	1.4520	1.0000	1.3330		
STD. DEV.	0.63348	0.85558	0.69104	0.86730	0.69616	0.84405		
MINIMUM	-0.875	-0.125	-0.875	-0.250	0.000	-0.250		
MAXIMUM	1.509	1.955	1.955	2.500	1.339	2.500		

[Sponsor's Table 7.3 Item 8, Vol. 1.92, p. 283]

APPEARS THIS WAY
ON ORIGINAL

Table 196. CHEOPS Area Under the Curve Minus Baseline (AUCMB) to the End

TABLE 7.4

CHEOPS AUCMB TO END

INTENT-TO-TREAT PATIENTS

VARIABLE	0.5% LEVOBUPIVACAINE			NO BLOCK			MEAN DIFFERENCE (95% CI) (1)	P-VALUE (2)
	UNILATERAL	BILATERAL	OVERALL	UNILATERAL	BILATERAL	OVERALL		
N	15	5	20	12	3	15	-0.5	0.030
MEAN	0.5238	0.1376	0.4272	0.9109	1.0863	0.9460	(-1.0, -0.1)	
MEDIAN	0.5170	0.0630	0.3540	1.0275	1.6210	1.1380		
STD. DEV.	0.68479	0.36746	0.63516	0.69474	0.94083	0.71482		
MINIMUM	-0.875	-0.217	-0.875	-0.250	0.000	-0.250		
MAXIMUM	1.558	0.708	1.558	2.088	1.638	2.088		

[Sponsor's Table7.4 Item 8, Vol. 1.92, p. 283]

APPEARS THIS WAY
ON ORIGINAL

Volume of Rescue Analgesia

The amount of morphine administered as rescue analgesia was not statistically significantly different between the two treatment groups. The mean volume of morphine used in the 0.5% levobupivacaine group was 1.97 mL compared with 2.29 mL in the no block group. One child in the no block group also received ketorolac.

Table 197. Volume of Rescue Analgesia

TABLE 8

AMOUNT OF RESCUE MEDICATION

INTENT-TO-TREAT PATIENTS

VARIABLE	0.5% LEVOBUPIVACAINE			NO BLOCK			PROPORTION DIFFERENCE (95% CI) (1)	P-VALUE (2)
	UNILATERAL N (%)	BILATERAL N (%)	OVERALL N (%)	UNILATERAL N (%)	BILATERAL N (%)	OVERALL N (%)		
PATIENTS RECEIVED MORPHINE								
YES	6/15 (40.0%)	3/ 5 (60.0%)	9/20 (45.0%)	9/12 (75.0%)	2/ 3 (66.7%)	11/15 (73.3%)	-0.283 (-0.052, 0.625)	0.167
NO	9/15 (60.0%)	2/ 5 (40.0%)	11/20 (55.0%)	3/12 (25.0%)	1/ 3 (33.3%)	4/15 (26.7%)		
MORPHINE (mg) (2)								
N	6	3	9	9	2	11		
MEAN	2.650	0.617	1.972	2.306	2.200	2.286		
MEDIAN	2.350	0.550	1.200	2.400	2.200	2.400		
STD. DEV.	1.8216	0.1607	1.7648	1.1870	0.2828	1.0663		
MINIMUM	1.00	0.50	0.50	0.85	2.00	0.85		
MAXIMUM	6.00	0.80	6.00	3.90	2.40	3.90		

(1) CI from Exact 95% CI from StatXact-3.

(2) P-value from Fisher's Exact test.

(3) Patients who used any morphine, total morphine volume.

(4) Patients who used any ketorolac, total ketorolac volume.

PROJECT16: [CHIRO5908.TABLES]T08.SAS 17:13 December 22, 1997

Reference: LISTING 8

[Sponsor's Table 8., Item 8, Vol. 1.92, p. 285]

Table 198. Volume of Rescue Analgesia (continued)

TABLE 8

AMOUNT OF RESCUE MEDICATION

INTENT-TO-TREAT PATIENTS

VARIABLE	0.5% LEVOBUPIVACAINE UNILATERAL n (%)	0.5% LEVOBUPIVACAINE BILATERAL n (%)	0.5% LEVOBUPIVACAINE OVERALL n (%)	NO BLOCK UNILATERAL n (%)	NO BLOCK BILATERAL n (%)	NO BLOCK OVERALL n (%)	PROPORTION DIFFERENCE (95% CI) (1)	P-VALUE (2)
PATIENTS RECEIVED KETOROLAC								
YES	0	0	0	1/12 (8.3%)	0	1/15 (6.7%)	-0.057 (-0.206, 0.414)	0.429
NO	15/15 (100.0%)	5/ 5 (100.0%)	20/20 (100.0%)	11/12 (91.7%)	3/ 3 (100.0%)	14/15 (93.3%)		
KETOROLAC (mL) (3)								
N	0	0	0	1	0	1		
MEAN				23.0		23.0		
MEDIAN				23.0		23.0		
STD. DEV.								
MINIMUM				23		23		
MAXIMUM				23		23		

(1) CI from Exact 95% CI from StatXact-3.
(2) P-value from Fisher's Exact test.
(3) Patients who used any morphine, total morphine volume.
(4) Patients who used any ketorolac, total ketorolac volume.

PROJECT16: [CHIRO5908.TABLES]T08.SAS 17:13 December 22, 1997 Reference: LISTING 8

[Sponsor's Table 8, Item 8, Vol. 1.92, p. 286]

Time to First Request for Rescue Medication

The time to first request for rescue medication was significantly longer in the 0.5% levobupivacaine group compared with the no block group. The median patient in the 0.5% levobupivacaine group first requested rescue medication at least 118 minutes following Time 0 compared with 31 minutes in the no block group (p=0.041).

Table 199. Time to First Request for Rescue Medication

TABLE 6.3

TIME TO FIRST USE OF RESCUE MEDICATION

INTENT-TO-TREAT PATIENTS

VARIABLE	0.5% LEVOBUPIVACAINE(1)	NO BLOCK(1)	P-VALUE(2)
TIME TO FIRST REQUEST FOR RESCUE MEDICATION (min)			
N	20	15	0.041
QUANTILES			
25%	47.5	27.0	
50%	NE	31.0	
75%	NE	NE	
NUMBER OF CENSORED OBSERVATIONS	11	4	

[Sponsor's Table 6.3, Item 8, Vol. 1.92, p. 270]

TABLE OF CONTENTS

1.0 INTRODUCTION

In response to an approvable letter dated, 2/24/99, the sponsor has submitted safety data from four clinical trials not previously submitted to the NDA and constitutes safety data obtained since the 120-day safety update. Information from these four clinical trials (240-day safety update), the 120 day safety update (submitted 8/27/98), as well as integrated summary of safety (ISS) have been incorporated into the final printed label for levobupivacaine.

2.0 BACKGROUND

2.1.1 Drug History

2.1.1.1 Marketed Drug History

The rationale for development of levobupivacaine injection, the S(-)- enantiomer form of bupivacaine, was based upon findings indicating that there is anesthetic stereospecificity of action of the cardiac effects, with the S(-)- enantiomer having significantly less cardiotoxicity yet similar potency to bupivacaine.

2.1.1.2 Administrative History - ALSAC

In response to a Chiroscience request that the warning label for bupivacaine concerning the use of 0.75% in obstetric patients not be applied to their product – levobupivacaine, the Anesthetic and Life Support Drugs Advisory Committee in 1997 made the following recommendations. Below please find the Anesthetic and Life Support Drugs Advisory Committee recommendation followed by the Agencies appraisal of the sponsor's response.

I. ALSAC

Safety of levobupivacaine must be demonstrated over several animal models

FDA

The pharmacology reviewer, Dr. A. Goheer, upon analysis of the preclinical data submitted for the NDA, found evidence of an improved cardiovascular safety profile over the racemate - bupivacaine. Support for this conclusion was found in the following data:

1) Pig intracoronary administration of levobupivacaine (lethal dose ~ 8mg), bupivacaine (lethal dose ~ 5mg), or ropivacaine (lethal dose similar to levobupivacaine) and,
2) QRS prolongation occurred at higher doses of levobupivacaine than bupivacaine following pig intracoronary drug administration.
3) Sheep median plasma levels associated with ventricular tachycardia leading to fatal ventricular fibrillation occurred at 300-350 mg of levobupivacaine versus 150-200 mg of bupivacaine, and
4) Sheep median plasma levels that lead to cardiovascular collapse was 5 ug/ml of levobupivacaine versus 2 ug/ml of bupivacaine
5) *in vitro* electrophysiological and contractility data

However, to substantiate the sponsor's claims of safer cardiovascular and CNS profiles, the essential questions to answer are the following:

1) Does levobupivacaine directly effect the myocardium and/or CNS
2) Does the CNS play a role in cardiotoxicity?
3) Does levobupivacaine – induced cardiorespiratory arrest demonstrate similar difficulty of resuscitation in the animal

The recommended studies that best answer these questions are the following:

1) Direct carotid artery infusion (cardiac performance maintained),
   a) *The intra-carotid and the resuscitation studies in sheep have not been started.*
2) Heart-direct coronary artery infusion (CNS performance maintained), and
   a) *The coronary artery infusion studies with the levobupivacaine, bupivacaine, and ropivacaine in sheep have been completed.*
3) A study on resuscitation following cardiovascular infusion.
   a) *The experimental phase of dog resuscitation study has been completed.*

In conclusion, the Division Director made the following statement, " the early preclinical work being quite compelling suggests a strong theoretical basis for postulating a differential toxicity between racemic bupivacaine and the enantiomer on cardiovascular toxicity. How this unquestionable, theoretical advantage translates into a clinically meaningful advantage is yet to be answered."[1]

II. ALSAC

Safety of levobupivacaine must be demonstrated in at least one clinical study that demonstrates at least a 25% increase in safety over bupivacaine, as shown by a shift in the toxicokinetic curve (lidocaine controls were also suggested)

FDA

Statistician, Tom Permutt, Ph.D., upon review of the preclinical and clinical trial results, concluded that the sponsor had definitely demonstrated a 25% increase in safety of levobupivacaine over bupivacaine, however there was no data to suggest that the product was also more potent. Therefore, the actual risk – to – benefit ratio has yet to be answered.

III. ALSAC

Further definition of the nature of the cardiac arrhythmias seen in levobupivacaine in a human model

FDA

No data has been submitted which addresses this issue.

[1] Quotation from "Opening Remarks", Dr. McCormick, p. 11, Anesthetic and Life Support Drugs Advisory Committee meeting 1/12/99.

IV. ALSAC

Patients younger than 6 months be studied separately from older patients (groups of 2 to 5 years and 6 to 12 years) and that a comparison of caudal/epidural continuous infusions is necessary to determine the toxicity levels in children. An open label study, with or without pharmacokinetic subsets, is appropriate for the pediatric population.

FDA

The sponsor has yet to submit a clinical trial of this design.

Upon review of the NDA, it was decided that a second Anesthetic and Life Support Drugs Advisory Committee meeting was needed to provide advice to the Food and Drug Administration about the risk-to-benefit ratio of levobupivacaine. It was held on January 12, 1999. The committee was provided with the pertinent data from the NDA asked the following questions (1) does the existing data support a lesser warning than exists for bupivacaine? (2) if so, what evidence is most compelling, (3) should further studies be undertaken, (4) will satisfactory completion of the preclinical studies yet to be performed contribute to changes in the warnings that currently exist in the bupivacaine label for this product?, (5) does the preclinically demonstrated dose separation for toxicity extrapolate in a practical way to humans, (6) at what doses does one expect to see significant cardiovascular toxicity and at what concentrations and settings, (7) will cardiovascular toxicity be achieved in the normal course of anesthesia[2]

While all of these Food and Drug Administration questions were not specifically answered, the following is a synopsis of the final conclusions of the January 1999 Anesthetic and Life Support Drugs Advisory Committee meeting.

Box Warning

The final recommendation with respect to the box warning was to remove the box warning from both levobupivacaine and bupivacaine and to replace it with a warning statement similar to that seen in the ropivacaine label which outlines the appropriate dose and management of obstetric patients.

Cardiac Toxicity

In response to the question, "has the sponsor adequately evaluated levobupivacaine's potential for cardiac toxicity...if not, what further studies are needed?", the committee in general agreed that the, "...we will never get the perfect human toxicity study, so I think they've done as much as is reasonable to learn about this."[3]

25% Increase in Safety of Levobupivacaine

With respect to the committee's previous request to the sponsor in 1997 to document at least a 25% increase in the safety" ...of levobupivacaine..."over bupivacaine in a clinical study, the general consensus was that the sponsor had shown this in the animals but not in humans and that it would be difficult to do so in humans.

Pending Data

The committee expressed concern over the lack of data on resuscitation, hepatic dysfunction and ethnicity, and insufficient data on pediatric/newborn toxicity, gender, potency differences between levobupivacaine and bupivacaine, and drug interactions.

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[2] Quotation from "Opening Remarks", Dr. McCormick, pp. 12-13, Anesthetic and Life Support Drugs Advisory Committee meeting 1/12/99.

[3] Quotation from "Committee Vote", Dr. Reves, p. 240, Anesthetic and Life Support Drugs Advisory Committee meeting 1/12/99.

In closing, the division posed the following questions to the sponsor: "...where do the resuscitation studies stand and ...can we expect them as a phase IV commitment", and "...do you have plans for exposure down to newborns"[4]. The sponsor's response was the following: the experimental phase of the dog study (resuscitation study) is done and being analyzed and will be submitted as a final report to the Agency as soon as we can, and a pediatric study report will be submitted within the next few weeks.

SCOPE AND DESIGN OF THE DEVELOPMENTAL PROGRAM

3.0 CHEMISTRY

Please note NDA 20-997 for details.

4.0 ANIMAL PHARMACOLOGY

Please note NDA 20-997 for details.

5.0 Description of Clinical Data Sources (Populations Exposed and Extent of Exposure)

This 240-day safety update includes four clinical trials conducted both in the US and Europe, with a total exposure of 325 patients and subjects. It includes one Phase I trial consisting of 8 male subjects exposed to a maximum dose of 50 mg intravenous levobupivacaine (25 mg levobupivacaine and 25 mg deuterium-labeled levobupivacaine).

In addition, there are three Phase III trials consisting of 262 patients exposed to levobupivacaine and 55 patients exposed to bupivacaine. These trials consisted of two epidural labor trials, as follows: (1) Study 030627 consisted of 37.5 mg maximal, epidural, bolus doses of 0.25% levobupivacaine (N=56) vs. 0.25% bupivacaine (N=55) administered to women in labor followed by a continuous infusion of 0.125% levobupivacaine or bupivacaine at 12ml/h. The mean infusion rate was 28 mg/h – levobupivacaine and 27 mg/h – bupivacaine, and (2) Study 030449 was a trial designed to determine the minimum dose of levobupivacaine (0.02-0.13%, or 4-26 mg) with or without fentanyl (2 or 3 μg/ml) needed to control labor pain (N=106). The mean dose of levobupivacaine administered was not provided. The third trial consisted of an interscalene block administration of 150 mg maximal dose of 0.5% levobupivacaine (N=100).

In an effort to ensure precise estimations of the incidence of adverse events occurring in the clinical trials, the following pooling of studies were made according to anesthetic/surgical procedure performed:

[4] Quotation from "Opening Remarks", Dr. McCormick, pp. 254-255, Anesthetic and Life Support Drugs Advisory Committee meeting 1/12/99.

Phase I

- single center, open labeled trial (N=8)
- pharmacokinetic effects of intravenous deuterium-labeled levobupivacaine when administered simultaneously with unlabeled levobupivacaine.
- levobupivacaine (25 mg) and deuterium-labeled levobupivacaine (25 mg)

Phase III

<u>Two Obstetrical Studies:</u>

Two labor epidural – double blind, randomized

1. 0.25% levobupivacaine (N=56) vs. bupivacaine followed by 0.125% infusion (N=55)
2. 0.02%-0.13% levobupivacaine ± 2 or 3 μg/ml fentanyl
    a) levobupivacaine - N=40,
    b) levobupivacaine + fentanyl 2μg/ml - N=34,
    c) levobupivacaine + fentanyl 3μg/ml - N=32

<u>Interscalene Block Studies</u>

Open label, randomized, noncomparative (N=100)

0.5% levobupivacaine - 150 mg (max)

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pages of trade

secret and/or

confidential

commercial

information

7.0 Integrated Review of Safety

8.0 Methods and Findings for Safety Review

The format used in this analysis is a side by side comparison of the contribution made by the 240-day safety update to the 120-day safety update. This review will reference as needed and serve as a continuum of the NDA (integrated summary of safety) and 120-day safety update.

The levobupivacaine 240-day safety update includes a total of 4 trials conducted in the U.S. and abroad involving 325 patients. Of the 328 patients enrolled, 325 (99%) were treated and evaluable for safety. The safety population for the 120-day safety update is presented statistically alongside that for the 240-day safety update.

To correlate with current clinical practice and best determine the safety of levobupivacaine, the review of this data is presented according to categories of anesthesia technique, i.e., epidural anesthesia, interscalene block, as well as a separate section for the pharmacokinetic trial.

8.1.1 Deaths – All Studies

8.1.1.1 Methods

8.1.1.2 Sponsor's Methods

No description was provided of the sponsor's rules for including deaths for consideration in the 240-day safety update. Available for review were case report forms, narrative summaries, and case report tabulations.

8.1.1.3 Reviewer's Methods

8.1.1.3.1 Reviewers Analysis

The sponsor has not provided an analysis of deaths; therefore, an in depth analysis of the narrative summaries and case report tabulations for each death was performed by this reviewer. All events provided surrounding each death, e.g., time and date of death, dosing, medical and surgical histories, concomitant medications, surgical intervention and complications, etc. were analyzed and tabulated.

8.1.1.4 Results

A total of two deaths occurred in the levobupivacaine development program - one in the NDA and one in the 240-day safety update. Please note the NDA medical review for details of the death occurring in the NDA.

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Case Narrative – Interscalene Block

52-year-old white female with a history of cardiac murmurs [Note: unspecified type] and hyperthyroidism received 0.5% levobupivacaine preoperatively for excision of the left clavicle and acromioplasty. 4.3 hours post-exposure, the patient developed intermittent hypotension and sinus bradycardia for which she was treated with ephedrine and phenylephrine. The bradycardia resolve in 15 minutes; however, the hypotension persisted. It eventually resolved 3.6 hours after its onset.

There are two possible etiologies of the hypotension and bradycardia, namely, (1) the patients preexisting cardiac murmur (assuming valvular heart disease) or/and (2) drug-induced. The patient received multiple medications throughout her hospital course including, levobupivacaine, phentermine, midazolam, succinylcholine, thiopental, cisatracurium, isoflurane, nitrous oxide, glycopyrrolate, neostigmine, droperidol, ketorolac, oxycodone, propoxyphene with acetaminophen, ephedrine and phenylephrine, some of which - alone or in combination – could have contributed to the serious adverse events. Therefore, it would be problematic and inaccurate to point to any one of these two possible etiologies as the more likely source of the serious adverse events.

8.1.3 ASSESSMENT OF DROPOUTS

8.1.3.1 · Levobupivacaine Exposure

A. Phase I Studies

No significant changes in the mean doses of levobupivacaine and bupivacaine occurred with the addition of the eight male subjects of this 240 - Day Safety Update. In addition, none of the eight males discontinued prematurely. Please note table below.

Table 3. Levobupivacaine Exposure – Phase I Studies

	LEVOBUPIVACAINE (120-Day Update) N=71	LEVOBUPIVACAINE (240-Day Update) N=79[5]
Mean ±SD	41 ± 26	42 ± 39
Min-Max	6.3-150	6.3-150

[5] Represents the 71 patients from the 120-Day Update plus the 8 additional 240-Day Safety Update subjects.

B. Phase III Studies

In the phase III studies, patients received the following:

(1) levobupivacaine vs. bupivacaine bolus followed by a continuous infusion (epidural for labor),
(2) levobupivacaine with fentanyl 2/3 μg/ml epidurally for labor, and
(3) levobupivacaine administered via interscalene block.

The mean dose of levobupivacaine (99.80mg to 99.89mg) and bupivacaine (98.75mg to 94.29mg) administered by bolus injection did not change significantly since the 120-day safety update. More dramatic changes were seen in the category, "levobupivacaine + other" [Note: "other" refers to narcotics such as, morphine and fentanyl and clonidine] in which the mean dose changed from 137.50 mg (120 day safety update) to 97 mg (240 - Day Safety Update). Please note sponsor's table below for details.

Anesthesia category-specific data of the mean doses administered per trial were not provided; therefore, the mean dose delivered by infusion is unknown.

Table 4. Dosages of Levobupivacaine, Bupivacaine and Levobupivacaine + Other: Phase III Studies

	Levobupivacaine 120 - Day Safety Update N=732	Levobupivacaine 240 - Day Safety Update N=928	Bupivacaine 120 - Day Safety Update N=398	Bupivacaine 240 - Day Safety Update N=453	Levobupivacaine + Other 120 - Day Safety Update N=147	Levobupivacaine + Other 240 - Day Safety Update N=213
Mean ± SD	99 ± 55	99 ± 55	98 ±48	94 ± 47	137 ± 37	97 ± 66
Min-Max	10-300	10-300	10-202	10 –202	75-375	4-375

(adapted from Sponsor' s Table 5, item 8, vol. 18.1a, p. 130)

No patients were discontinued due to adverse events.

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9.3 SUMMARY OF POTENTIAL ADVERSE EVENTS CONSIDERED RELATED TO STUDY DRUG

No new data has been provided.

10.0 CONCLUSIONS

The data presented in this 240 - Day Safety Update is consistent with the existing safety database.

Based upon review of the data submitted, levobupivacaine appears to be reasonably safe when used as recommended. However, with respect to claims of improve cardiovascular safety over that of bupivacaine, the sponsor has not provided sufficient evidence to prove this, decisively.

11.0 RECOMMENDATIONS

In the opinion of this reviewer, NDA 20-997 should be approved.

/S/

Monica L. Roberts, M.D.
Medical Reviewer
July 22, 1999

/S/ 8/5/99

Bob Rappaport, M.D.
Deputy Division Director

FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
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REVIEW and EVALUATION of CLINICAL SAFETY DATA

NDA:	**20-997**
SPONSOR:	**DARWIN DISCOVERY LTD (PAREXEL)**
DRUG:	**CHIROCAINE (LEVOBUPIVACAINE) INJ.**
PROPOSED INDICATION:	**SURGICAL ANESTHESIA/ PAIN CONTROL**
CLINICAL REVIEWER:	**MONICA L. ROBERTS, M.D.**
ORIGINAL RECEIPT DATE:	**April 29, 1998** **August 27, 1998**
DATE of REVIEW:	**February 25, 1999**
MATERIALS RECEIVED:	**NDA- 20-997** Safety Update and **Amendment to NDA: 120 Day Safety Update**
PROJECT MANAGER:	**SUSMITA SAMANTA, MD**

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1.0 Introduction

The original NDA safety data is herein reviewed for the product, levobupivacaine, the S-enantiomer of marketed bupivacaine (approved 1972). Also included is a review of the 120 day final safety update report.

The associated prolonged blockade of cardiac sodium channels and subsequent depression of electrophysiological response, i.e., decreases in myocardial contractility and rate of conduction of cardiac electrical impulses, seen with bupivacaine has prompted a rash of clinical evaluations of alternative long–acting local anesthetics, e.g., levobupivacaine and ropivacaine.

Specifically, bupivacaine is thought to cause a reentrant type of dysrhythmia similar to a torsades de pointes dysrhythmia (a type of ventricular tachycardia associated with prolonged QT intervals). The increased cardiotoxicity of bupivacaine is thought to result from both a direct action on the heart as well as an indirect action on the CNS. The human experience with levobupivacaine will herein be evaluated with emphasis on drug-induced cardiovascular abnormalities as well as predictable local anesthetic side effects.

Twelve preclinical studies designed to evaluate the potential cardiotoxicity of levobupivacaine were conducted -5 prospective and 7 published reports. The routes of administration included intracoronary (pigs), intravenous (rat and sheep) and *in vitro* (human, guinea pig, and rabbit cardiac tissue). When given intravenously, findings of a net decrease in cardiac output at high dosages, decrease left coronary blood flow, bradycardia, tachycardia, hyper- and hypotension, convulsions, increase QRS width, supra- and ventricular arrhythmias, bigeminy and trigeminy, and death were evident in both the levobupivacaine and bupivacaine treated animals. However, there was evidence of a more favorable cardiac response following levobupivacaine exposure.

Additionally, changes in electrophysiological parameters, e.g., QRS, QTc and PQ intervals, were evaluated in pigs given levobupivacaine, bupivacaine or ropivacaine via the left anterior descending coronary artery which showed some differences in dose-dependent interval increases in favor of levobupivacaine. There were also significant differences in the LD_{50} in favor of levobupivacaine.

2.0 Materials Utilized in Review

Received	4/29/98:	NDA 20-997
	8/27/98:	Amendment to the NDA: Item 9. Safety Update (120 Days)
		Amendment to the NDA: Response to FDA Requests at Pre-NDA Meeting (3/17/98)
		Case Report Forms and Tabulations (NDA 20-997, Vol. 1.158)
		Integrated Summary of Safety (NDA 20-997; Vol. 1.97)
	1/7/97	IND
Dated	3/24/97	ALSAC Meeting Transcripts

2.1 Related Reviews and Consults for the NDA

Received	12/3/98	Cardiology Consultant: John P. DiMarco, M.D., and Ph.D. Director, Clinical Electrophysiology Laboratory Associate Division Head, Cardiovascular Division Department of Medicine The University of Virginia

3.0 Background

3.1 Indication - Surgical Anesthesia and Pain Management

3.2 Important Information from Related INDs and NDAs and from Pharmacologically Related Agents

Ropivacaine, a currently available local anesthetic, was developed based upon the premise of stereospecificity of cardiac effects, with the l-isomer having equal potency but less cardiotoxicity than the d-isomer. Initial human studies indicate ropivacaine to have similar potency and duration to bupivacaine;[1] however, the risk of cardiovascular toxicity has not been completely eliminated.

[1] Akerman Bupivacaine, Hellberg I-Bupivacaine, Trossvik C: Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103). Acta Anaesthesiol Scand 32:571, 1988

3.3 Administrative History

In compliance with the recommendations made by the Anesthetics and Life Support Advisory Committee to the FDA in 1983, a guidance document was published which stated that approved drugs must be studied to (1) determine the effective anesthetic dose (with the appropriate preclinical and clinical pharmacokinetic evaluations); (2) determine the safe doses following intravenous infusion and multiple bolus injections; (3) determine the arrhythmogenic potential in both pregnant and nonpregnant animal models[2] and the electrophysiologic mechanism in isolated tissue; and , lastly, (4) determine the nature of resuscitation.

Pursuant to a request from the sponsor of levobupivacaine to not include the box warning as currently written for bupivacaine, which addresses accidental intravascular injection of 0.75% bupivacaine, the Division posed the following three questions to the Anesthetics and Life Support Advisory Committee:

1. What kind and quality of data would be required to remove the box warning from levobupivacaine? The committee's recommendations were as follows (Note: sponsor's fulfillment of these recommendations or lack thereof can be found in italics):

    a. Safety of levobupivacaine must be demonstrated over several animal models,
        i. *Fulfilled: Animal models studied include pig, sheep, guinea pig and rat*

    b. Safety of levobupivacaine must be demonstrated in a least one clinical trial that demonstrates at least a 25% increase in safety over bupivacaine, as shown by a shift in the toxicokinetic curve,
        i. *Fulfilled: Study 004801 was a double blind, randomized, crossover study in subjects dosed with intravenous bupivacaine or levobupivacaine to CNS symptomatology. Dosages for which CNS symptoms were seen were 150 mg of levobupivacaine and 110 mg of bupivacaine.*

    c. Further definition of the nature of the cardiac arrhythmias seen with bupivacaine
        i. Unfulfilled - No formal analysis was made of the bupivacaine – induced cardiac arrhythmias – neither the nature, resuscitatibility nor inducibility thereof

2. Can the committee make any recommendations regarding the specific studies, patient populations, or treatment settings needed to evaluate the risk of levobupivacaine in its anticipated clinical usage? The committee's recommendations were as follows:

    a. Initial studies on safety should avoid using patients with histories of cardiovascular disease, and,
        i. Fulfilled: No patients with evidence of cardiovascular disease were included in the study; however, there were cases of preexisting, asymptomatic cardiovascular conditions.

    b. Studies that include cycling females with high progesterone levels would be preliminary to allowing studies in obstetrics, and,
        i. Unfulfilled -The sponsor did not perform any preliminary studies of this kind prior to the four obstetric studies (2 labor epidural, 2 epidural for cesarean section) conducted in the NDA.

[2] This decision was based upon knowledge of the increased sensitivity of pregnant patients to the effects of local anesthetics.

c. Patients younger than six months should be studied separately from older patients and a comparison of caudal/epidural continuous infusions is necessary to determine the toxicity levels in children. An open label study with or without pharmacokinetic analyses is acceptable.

i. Unfulfilled -No patients younger than six months were studied.

3.4 Foreign Marketing

Chirocaine, (levobupivacaine injection) has not been approved for use in any country; however, it has a pending license in Sweden. It has been investigated in both animals and humans outside of the USA for a number of years. The IND[redacted]" A Double Blind Randomized Controlled Trial of 0.5% Levobupivacaine Compared to 0.5% Bupivacaine for Epidural Anesthesia in Patients Undergoing Elective Cesarean Section" was submitted to allow the initiation and completion of the Phase III program in the U.S.

A United States use patent for levobupivacaine was obtained on January13, 1998 for experimental use of the product. Transthoracic electrical bioimpedance technique was used to estimate myocardial contractility index and stroke index for levobupivacaine and racemic bupivacaine in healthy male subjects. From these measurements, the preferred use of levobupivacaine is suggested for patients having depressed myocardial contractility.

4.0 Chemistry , Manufacturing, and Controls

Levobupivacaine (S-enantiomer of bupivacaine) is chemically described as (S)-l-butyl-2-piperidylformo-2',6'-xylidide hydrochloride. It is a sterile, non-pyrogenic isotonic aqueous solution containing Levobupivacaine HCl equivalent to 2.5 mg/mL, 5.0 mg/mL, and 7.5 mg/mL of Levobupivacaine base.

Despite findings of similar physico-chemical properties, clinical trials with levobupivacaine were conducted with less than 0.2% of the R-enantiomer. Therefore, this same level of purity (99.8%) has been recommended by the Division's reviewing chemists for marketing.

Additionally, the solvent used safely in clinical trials was isopropranolol (254ppm), methyl tertiary butyl ether (1 ppm) and isopropyl acetate (1 ppm). For distribution, the sponsor has requested substituting for toluene. The Division's reviewing pharmacologists is in agreement with this substitution and has recommended 50 ppm.

5.0 Animal Pharmacology and Toxicology

The pharmacology reviewer, Dr. A. Goheer, upon analysis of the preclinical data submitted for this NDA, found evidence of a improved cardiovascular safety profile over the racemate - bupivacaine. Support for this conclusion was found in the following data:

1) Pig intracoronary administration of levobupivacaine (lethal dose ~ 8mg), bupivacaine (lethal dose ~ 5mg), or ropivacaine (lethal dose similar to levobupivacaine) and,
2) QRS prolongation occurred at higher doses of levobupivacaine than bupivacaine following pig intracoronary drug administration.
3) Sheep median plasma levels associated with ventricular tachycardia leading to fatal ventricular fibrillation occurred at 300-350 mg of levobupivacaine versus 150-200 mg of bupivacaine, and
4) Sheep median plasma levels that lead to cardiovascular collapse was 5 ug/ml of levobupivacaine versus 2 ug/ml of bupivacaine
5) *in vitro* electrophysiological and contractility data

However, to substantiate the sponsor's claims of safer cardiovascular and CNS profiles, the essential questions to answer are the following:

1) Does levobupivacaine directly effect the myocardium and/or CNS
2) Does the CNS play a role in cardiotoxicity?
3) Does levobupivacaine – induced cardiorespiratory arrest demonstrate similar difficulty of resuscitation in the animal

The studies recommended to best answer these questions are the following:

1) Direct carotid artery infusion (cardiac performance maintained),
   a) *The intra-carotid and the resuscitation studies in sheep have not been started.*
2) Heart-direct coronary artery infusion (CNS performance maintained), and
   a) *The coronary artery infusion studies with the levobupivacaine, bupivacaine, and ropivacaine in sheep have been completed.*
3) A study on resuscitation following cardiovascular infusion.
   a) *The experimental phase of dog resuscitation study has been completed.*

Ultimately, the reviewer believes that the data submitted supports the reasonable safety of levobupivacaine for the proposed use in humans and therefore recommends approval of the product on the basis its pharmacology and toxicology profile.

The early preclinical work being quite compelling suggests a strong theoretical basis for postulating a differential toxicity between racemic bupivacaine and the enantiomer on cardiovascular toxicity. How this unquestionable, theoretical advantage translates into a clinically meaningful advantage is yet to be answered.

In the catheterized ewes studies for example, intravenous levobupivacaine was capable of causing the very same cardiovascular effects attributed to bupivacaine, but at a higher dose. Does this dose separation for toxicity extrapolate in a practical way to the human or clinical situations, at what doses does one expect to see significant human cardiovascular toxicity and at what concentrations, in what setting and finally, will toxicity be reached in the normal course of anesthesia or pain management - these are the questions the clinical trials must answer.

6.0 Description of Clinical Data Sources (Populations Exposed and Extent of Exposure)

In the original NDA, there were a total of 24 studies completed, both in the US and Europe, with a total exposure of 1395 patients. In the phase II/III studies there were 391 patients exposed to bupivacaine, 31 who received lidocaine with epinephrine and 47 who received placebo. The updated database includes an additional 3 studies including 33 patients (levobupivacaine N= 26 and bupivacaine N=7).

Complications in anesthesia follow lines of similarity, i.e., maternal hypotension, and/or fetal bradycardia can complicate all labor epidural anesthetics, whereas respiratory depression is more common in narcotic-based epidural infusions during pain management. Appropriately, in an effort to ensure meaningful estimations of the incidence of adverse events occurring in the clinical trials, pooling of studies were made according to the type of anesthesia performed.

orig - 24 stud, N=1395
-391-b;
120su = 3 stud 33 pts
26 = levo

Phase I

- Two pharmacokinetics studies
- Four pharmacodynamic studies –CNS, cardiovascular endpoints (intravenous administration) and peripheral nerve block endpoints

Phase II/III

Obstetrical Studies

Four Obstetrical Studies: Epidural Anesthesia

- 2 cesarean section and 2 labor epidural
- 0.07%-0.5% levobupivacaine vs. bupivacaine

Central Block Studies

Three Central Block Studies

- Epidural infusion for orthopedic (75 mg of 0.5% levobupivacaine, 112.5 mg of 0.75% levobupivacaine or 75 mg of 0.5% bupivacaine) and
- Epidural infusion for abdominal surgery (150 mg of 0.75% levobupivacaine or 150 mg of 0.75% bupivacaine)
- Subarachnoid injection for lower limb surgery (15 mg of 0.5% levobupivacaine) – open label

Four Central Block Studies – Post-operative Epidural Infusions

- 3 orthopedic, 1 major abdominal surgery – 75 - 150 mg bolus doses of 0.0625% - 0.25% levobupivacaine or bupivacaine followed by 4-10 ml/hr of infusions of 0.0625% - 0.25% levobupivacaine or bupivacaine.
- Three of the above studies included the co-administration of fentanyl, morphine or clonidine.

Peripheral Block Studies

Seven Peripheral Block Studies

- 2 Infiltration Nerve Block, 2 Brachial Plexus Block (one of which is ongoing), 2 Peribulbar Block, and 1 Inferior Alveolar Nerve Block
- Maximum dose of 150 mg and concentration of 0.75% of levobupivacaine or bupivacaine were administered
- Patients in the inferior alveolar nerve block study received 2% lidocaine with epinephrine vs. 0.75% levobupivacaine.

Pediatrics

Three Pediatric Studies (2 ongoing)

- Ilioinguinal-Iliohypogastric Nerve Bock – single blind, 1.25 mg/kg of 0.5% levobupivacaine vs. no treatment
- [illegible]
- Other

One Special Analysis Study

- Integrated analysis of signal average QT dispersion and QRS segments from ECG tracings
- Doses of 0.25%-0.75% levobupivacaine vs. bupivacaine given to both patients and healthy volunteers (administered to the onset of CNS toxicity)

6.1 Primary Source Data (Development Program)

6.1.1 Levobupivacaine Exposure

A total of 60 Phase I patients were exposed to intravenously administered levobupivacaine at a mean ± SD dosage of 36.41 ± 23.38 (min. 6.3 and max. 150.0). These studies were designed to find the dosages associated with the onset of CNS side effects. These were all short-term exposures.

In the Phase II/III studies, patients received a bolus epidural injection of levobupivacaine (up to 150 mg) to establish the block followed by further bolus injections or epidural infusions of study medication. The maximum dose of levobupivacaine administered via bolus in the levobupivacaine + other (other = fentanyl, morphine, clonidine) group was 375 mg (administered in divided doses) and 300 mg as a single bolus of levobupivacaine alone (Study CS 009, brachial plexus block).

A mean ± SD dose of 97.79 ± 48.88 mg of levobupivacaine was administered to 702 patients enrolled in the Phase II/III studies. By infusion, a total of 164 patients were exposed to a mean dose of levobupivacaine of 210.44 ± 111.68 mg. These were all short-term exposures.

Table 1

Enumeration of Subjects/Patients for Levobupivacaine Development Program (adapted from sponsor's tables)				
Study Groups	**Treatment Groups**			
	Levobupivacaine		**Bupivacaine**	
Completed Phase 1 – Intravenous Infusion and Ulnar Nerve Block[3]				
	S-bupivacaine (ISS) N=60	**S-bupivacaine (Update) N=71**	**Bupivacaine (ISS) N=58**	**Bupivacaine (Update) N=80**
Mean Dose ± SD	36 ± 23	41 ± 26	33 ± 20	51 ± 39
Minimum	6	150	12	12
Maximum	150	6	110	240
Completed Phase 2-3 – Dosages of Levobupivacaine and Bupivacaine (mg) Administered by Bolus Injection				
	S-bupivacaine (ISS) N=702	**S-bupivacaine (Update) N=732**	**Bupivacaine (ISS) N=391**	**Bupivacaine (Update) N=398**
Mean Dose ± SD	98 ± 49	100 ± 55	100 ± 48	99 ± 48
Minimum	10	10	10	10
Maximum	300	300	202	202
Completed Phase 2-3 by Category – Dosages of Levobupivacaine and Bupivacaine (mg) Administered by Bolus Injection: Peripheral Block Studies				
	S-bupivacaine (ISS) N=210	**S-bupivacaine (Update) N=224**	**Bupivacaine (ISS) N=146**	
Mean Dose ± SD	100 ± 51	112 ± 66	104 ± 43	
Minimum	34	34	37	
Maximum	300	300	196	
Completed Phase 2-3 by Category – Dosages of Levobupivacaine and Bupivacaine (mg) Administered by Bolus Injection: Pediatric Block Studies				
	S-bupivacaine (ISS) N=20	**S-bupivacaine (Update) N=36**	**Bupivacaine (ISS) N=7**	
Mean Dose ± SD	32 ± 14	31 ± 15	32 ± 10	
Minimum	13	12	20	
Maximum	67	75	47	
Completed Phase 2-3 by Category – Dosages of Levobupivacaine and Bupivacaine (mg) Administered by Bolus Injection: Bupivacaine – Controlled Phase 2-3 Studies				
	S-bupivacaine (ISS) N=445	**S-bupivacaine (Update) N=453**	**Bupivacaine (ISS) N=391**	**Bupivacaine (Update) N=398**
Mean Dose ± SD	101 ± 46	100 ± 46	100 ± 48	99 ± 48
Minimum	10	10	10	10
Maximum	202	202	202	202

[adapted from sponsor's Tables 4-8, Safety Update, Vol. 1, pp. 037-040)

[3] Study 005276 – Double blind randomized contralateral ulnar nerve block study comparing 0.125%, 0.25% and 0.5% levobupivacaine to 0.25% bupivacaine in 20 healthy adult Caucasian males.

7.0 Human Pharmacokinetics and Pharmacodynamics

Twelve human studies of levobupivacaine pharmacokinetics have been submitted with data from two hundred and thirty four subjects. The reviewing pharmacokineticist, Suresh Doddapaneni, PhD's impression of the quality and content of these studies is as follows, "Human metabolism, excretion and protein binding of levobupivacaine have been adequately studied. Overall, in all these studies, the pharmacokinetics of levobupivacaine and bupivacaine were similar."

8.0 Integrated Review of Safety

8.1 Methods and Findings for Safety Review

The levobupivacaine development program included a total of 27 studies, conducted both in the US and Europe, with a total exposure of 1439 patients. In addition, there were 391 active-controlled patients who received corresponding doses of bupivacaine in phase II/III studies, 31 who received lidocaine with epinephrine and 47 who received placebo. Since April 29,1998, the date of the original NDA submission, data from fifty-nine additional patients have been reported in the 120-Day Safety Update. Forty-one of these patients received levobupivacaine (16 pediatric and 25 adult patients). Eleven of the remaining 18 bupivacaine-exposed patients, also received levobupivacaine as a single dose.

8.1.1 Deaths

There was one report of death in the levobupivacaine development program. This occurred in Patient 038 (Study 030742) who was a 70-year-old male with a medical history significant for a gastrointestinal disorder (treated with ranitidine) who received levobupivacaine and clonidine for left hip surgery. Pre-operative ECG demonstrated a left ventricular hemiblock – all other laboratory values were normal.

According to protocol, the patient received 15 milliliters of 0.75% levobupivacaine via epidural catheter. Subsequently, he received a second and third epidural injection (total amount received not specified; protocol maximum is 5 ml) followed in three hours by a 6 ml/hr infusion of 0.125% levobupivacaine with 50 mcg/hr clonidine.

The post-treatment course was significant for hypotension – BP 85-93/53-61 (preoperative BP –130/85) for which ephedrine was given and bradycardia – HR 54-90 (preoperative HR – 86). The patient first became bradycardic within the first hour following treatment and remained bradycardic for the ensuing 27 hours, with heart rates in the 50s and 60s. Oxygen saturation remained within normal limits and ECG showed a left axis deviation consistent with preoperative findings.

The intraoperative course was significant for four hundred milliliters of blood loss for which no transfusion was required and for a total intravenous fluid administration of 1500 milliliters.

Postoperatively, at 27 hours, there was an episode of pyrexia (temperature of 37.4° C) recorded.

Patient was discharged from the hospital 2 days after treatment and died 9 days later. Although the patient's family refused a post-mortem, the cause of death was determined to be myocardial infarction, likely to be unrelated to study drug administration.

In view of the death occurring nine days after drug administration, the likelihood of a causal relationship is remote. It is accepted theory that anesthetic related deaths usually occur within the first 72 hours following exposure.

However, this case of prolonged bradycardia in a patient without preexisting bradycardia suggests a strong theoretical basis for postulating a levobupivacaine-induced toxicity – albeit non-lethal.

Since the original NDA submission there were no further reports of death.

Table 2. Deaths: All Studies

Study #	Subject Information (age, gender, indication)	Medical History	Treatment	AEs Preceding Death (by WHO classification)	Severity
030742	Subject 038, 70 years, Male, Post – Total Hip Replacement Pain	Peptic Ulcer Disease	0.75 % levobupivacaine followed by 0.125% levobupivacaine + clonidine	1. Hypotension 2. Fever 3. Death	1. Mild 2. Mild 3. Severe

8.1.2 Serious Adverse Events

A total of nine hundred and fifty patients were treated with levobupivacaine (alone or in combination) in the levobupivacaine development plan (i.e., Phase I – N=71; Phase II/III – N=732 alone and 147 in combination). Sixty (52 alone and 8 combination) of these patients were reported as having serious adverse events. The clear majority of these adverse events occurred in the obstetric population with a total of 14 cases of fetal distress and 32 cases of delayed delivery. Similar doses of study drug administered to all patients.

"Fetal distress" and "failure to progress" often resulted in emergency (non-elective) cesarean section as can typically be seen following local anesthetic administration to parturients. The frequency with which adverse events occurred was similar between the two treatment groups. Please see Appendix 1 for the sponsor's Table 33 "Summary of Patients Undergoing Non-elective Cesarean Section".

The investigators did not consider these events to be related to study drug administration. This is an unexpected finding it light of the typical frequency with which local anesthetics have been implicated in episodes of failure to progress and even fetal distress. The demonstrated tendency to cause fetal distress and failure to progress is further evidence in support for "Warning" labeling similar to that seen for bupivacaine and ropivacaine. The practitioner should be made aware that levobupivacaine is capable of causing the same type and degree of obstetric adverse events one typically sees with intermediate –acting local anesthetics.

Since the original NDA submission, seven additional serious adverse events from ongoing studies were reported. Six of these cases occurred in obstetrics and one pediatrics. Upon review of the case narratives, (see Appendix 2) the clear majority of reports were of cesarean sections secondary to failure to progress (5/7), which is consistent with findings in the original NDA submission. Not consistent, however, is the fact that *all of these newly reported cases occurred in the levobupivacaine treatment group.*

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8.1.3 Withdrawals Due to Adverse Events

Phase I Studies

Of the one hundred and sixty-five phase I patients receiving intravenous study medication, (levobupivacaine, bupivacaine or placebo) to the onset of CNS side-effects, only one patient was said to have withdrawn due to serious adverse events. The reason given for termination was facial tingling which was considered to be at least possibly related to levobupivacaine administration.

Phase II/III Studies

Eight of the total one thousand, three hundred and fifty-five study patients in the Phase II/III clinical trials were withdrawn due to an adverse event. Six of these eight patients had been exposed to levobupivacaine alone (4/8) or in combination (2/8).

A case by case analysis of the levobupivacaine withdrawals revealed the following information. Study 030475, in which patients received an epidural infusion of study drug for post-operative pain management, produced three of the eight (38%) reporting patients. In all three of these cases levobupivacaine was considered to be responsible for the adverse event. They are described below:

- Patient 0039 complaints of confusion, somnolence, and agitation where considered to be possibly related to study drug,
- Patient 0040 experienced severe bradycardia which was considered to be definitely related to study drug, and
- Patient 0149 complained of pain (definitely related) and paresthesias (possibly related).

Other cases for which levobupivacaine was implicated in adverse dropouts were as follows:

- Patient 002 demonstrated signs of CNS toxicity, e.g., slurred speech, drowsiness, and excitability, secondary to suspected intravascular injection of 19 ml of 0.75% levobupivacaine. No change in vital signs was noted throughout the event. Patient was treated successfully with thiopental.
- Patient 133 underwent a radical nephrectomy for renal carcinoma complicated by an intraoperative pneumothorax. While in recovery, she received a bolus dose of levobupivacaine with morphine and developed bradycardia and eventually asystole. The onset of these cardiovascular events in relationship to the episode of vomiting led the investigators to a vasovagal etiology for the bradycardia and asystole.
- Patient 0201 was noted to have a leg length discrepancy post-orthopedic surgery. She, incidentally, received levobupivacaine with fentanyl.

Two bupivacaine withdrawals occurred secondary to suspected intravascular injection. Both patients developed reversible CNS side effects.

Since the submission of the original NDA no additional withdrawals due to adverse events were reported.

Table 4.

Withdrawals Due to Adverse Events – Phase I Studies

Based Upon Sponsor's Table 2.1

VARIABLE	LEVOBUPIVACAINE N=71		BUPIVACAINE N=80		PLACEBO N=14	
	N	%	N	%	N	%
Dose	71	100	80	100	14	100
Completed Study	70	99	80	100	13	93
Terminated Prematurely	1	1.4	0		1	7
Reason for Termination						
Adverse Event	1	1.4	0		0	
Administrative	0		0		1	7

(based upon Sponsor's Table 2.1, Safety Update, Vol. 1, p. 088-091)

Table 5

Withdrawals Due to Adverse Events – Phase II/III Studies

Based Upon Sponsor's Table 2.2

VARIABLE	LEVOBUPIVACAINE N=732		BUPIVACAINE N=398		LEVOBUPIVACAINE PLUS OTHER N=147		PLACEBO N=47		2% LIDOCAINE + EPINEPHRINE N=31	
	n	%	n	%	n	%	n	%	n	%
Dose	732	100	398	100	147	100	47	100	31	100
Completed Study	616	84	327	82	122	83	47	100	31	100
Terminated Prematurely	116	16	71	18	25	17	0		0	
Reason for Termination										
Adverse Event	4	0.5	2	0.5	2	1	0		0	

(based upon Sponsor's Table 2.2, Safety Update, Vol. 1, p. 092-095)

Table 6.

Withdrawals due to Adverse Events – Phase II/III (sponsor's Table 22)

Table 22 Summary of Adverse Events: Phase II/III Studies

	Levo N=702		Bupi N=391		Levo + Other N=147		Placebo N=47		Lidocaine + Adrenaline N=31	
Number of Patients With:	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
At least one adverse event	512	(72.9)	263	(67.3)	143	(97.3)	31	(66.0)	20	(64.5)
At least one moderate or severe adverse event	287	(40.9)	139	(35.5)	89	(60.5)	30	(63.8)	18	(58.1)
At least one moderate or severe and at least possibly drug-related adverse event	142	(20.2)	66	(16.9)	68	(46.3)	17	(36.2)	6	(19.4)
At least one serious adverse event	52	(7.4)	36	(9.2)	8	(5.4)	0		0	
Deaths	0		0		1	(0.7)	0		0	
Discontinuations due to adverse events	4	(0.6)	2	(0.5)	2	(1.4)	0		0	

Notes: Abstracted from Statistical Table 8.2. Levo = levobupivacaine, Bupi = bupivacaine.

Sponsor's Table 22, Item 8, Vol. 1.97, p. 058]

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8.2 Overall Adverse Event Profile

Controlled Trials

The incidences of adverse events were compared with controls and the data was pooled for each category of study.

Overall, the cardiovascular system (35.5%) was associated with the highest total overall incidence of adverse events followed by "gastrointestinal disorders" (33.0%), "body as a whole" (32.3%) and "central and peripheral nervous systems" (19.6%). Please note Appendix III for the sponsor's Table 30 and 31 "Most Common Adverse Events".

Phase I Studies

When considering the pooled data from the phase I studies in which patients were dosed with either levobupivacaine, bupivacaine or placebo until the onset of CNS side effects, there was nearly twice as many patients reporting at least one adverse event in the bupivacaine group (N=35) than in the levobupivacaine group (N=19). This same overall trend was seen in a number of events that were considered to be moderate or severe in nature, i.e. levobupivacaine (N=3), bupivacaine (N=8). No adverse event was considered to be serious.

The clear majority of events occurred in the "central and peripheral nervous system disorders" which had an overall incidence of 24%. This included dizziness (levobupivacaine 3%, bupivacaine 19%), paresthesias (levobupivacaine 8%, bupivacaine 15%) and headache (levobupivacaine 4%, bupivacaine 7%). The second most common adverse event was tinnitus (levobupivacaine 1.4%, bupivacaine 12%).

Interesting is the finding that despite an intravenous route of administration, the incidence of adverse events was not significantly higher than those following more acceptable modes of administration.

No additional data was analyzed since the original NDA submission in this category.

Obstetric Studies

In the adverse event data from the pooled obstetric studies, in which levobupivacaine (N=184) was compared to bupivacaine (N=188), there were no significant differences in the number of patients reporting at least one adverse event between treatment groups, i.e., levobupivacaine (N=144) and bupivacaine (N=136). The more common events were hypotension (levobupivacaine 33%, bupivacaine 38%), anemia (levobupivacaine 23%, bupivacaine 19%), nausea (levobupivacaine 14%, bupivacaine 20%), and fetal distress (levobupivacaine 14%, bupivacaine 12%). No additional data was analyzed since the original NDA submission in this category.

Please note Appendix IV for the sponsor's Table 32 "Most Common Adverse Events".

Central Block Studies

The pooled central block studies compared levobupivacaine (N=109) to bupivacaine (N=57). The reports of adverse events occurring at a frequency of $\geq$ 5% and with at least a two-fold incidence compared to the active control (bupivacaine) were seen for headache (8%), bradycardia (7%), and albuminuria (7%). No additional data was analyzed since the original NDA submission in this category.

Please note Appendix V for the sponsor's Table 34 "Most Common Adverse Events".

Post-Operative Pain Management Studies

In the post-surgery pain management studies, patients received a bolus dose of levobupivacaine alone (N=179) or in combination (N=147) with either fentanyl, clonidine or morphine followed by an epidural continuous infusion of the same study drug. Hypotension (levobupivacaine 62%, bupivacaine 79%) was the most frequently reported adverse event and occurred with similar frequency between groups. However, the events that occurred with at least a two-fold incidence compared to the active control (bupivacaine) and at a frequency of ≥ 5% were urinary retention (17%), urinary incontinence (6%) and anemia (33.5%). No additional data was analyzed since the original NDA submission in this category.

Please note Appendix VI for the sponsor's Table 35 "Most Common Adverse Events".

Peripheral Block Studies

Since the original NDA submission, in which there were unexpected, treatment emergent, abnormal EKGs (bradycardia was not specifically reported) and a two-fold increase in the incidence of headache compared to the active control (bupivacaine), there has been an overall increase in the incidence of patients reporting at least one adverse event and a nearly two-fold increase in the incidence of pain (8%) in the levobupivacaine treatment group.

Please note Appendix VII for the sponsor's Table 36 "Most Common Adverse Events".

Table 7

From Most Common Adverse Events ≥ 5%: Peripheral Block Studies (based upon Sponsor's Table 19)

EVENT	Levobupivacaine (ISS) N=210	Levobupivacaine (Update) N=224	Bupivacaine (ISS) N=146
	n %	n %	n %
EKG abnormal	16 (8%)	16 (7%)	17 (12%)
Pain	9 (4.3%)	18 (8%)	7 (5%)
Headache	13 (6%)	14 (6%)	5 (3%)
At Least One Adverse Event	104 (49%)	118 (53%)	80 (55%)

(based upon Sponsor's Table 19, Safety Update, p.055)

Updated pharmacokinetic data obtained from peripheral block studies has been submitted for review. Analysis of this data was made by the reviewing pharmacokineticist, Suresh Doddapaneni, Ph.D. who states that, "...since full study reports have not been submitted, it is not possible to do a formal review of those studies." However, "....the data submitted did not raise any special safety concerns."

Pediatric Studies

Previous pediatric clinical investigations of levobupivacaine compared it to placebo when administered as a ilio-inguinal nerve block for post-operative pain control. Three cardiovascular adverse events occurred, i.e., premature ventricular contractions (2) and bradycardia, but were said to have occurred prior to study drug administration. No trends were demonstrated through comparisons of the adverse events between the two groups.

Subsequently, ongoing, bupivacaine-controlled trials are underway to evaluate the caudal administration of the product. Preliminary data has been submitted for 23 patients.

When analyzing this data there is an obvious discrepancy in the population sizes, which makes interpretation of the study results difficult, at least from a comparative point of view. It would appear that, in multiple categories, levobupivacaine was associated with a two-fold increase in the incidence of adverse events; however, there are more than twice as many patients exposed to levobupivacaine (N=36) than bupivacaine (N=7).

It is possible to glean some useful information when examining the data submitted for levobupivacaine-exposed patients alone. One sees that the same adverse events reported in the original submission (N=20) were also present in the updated information (N=36) but with increased frequency. Also, as was seen in the original submission, similar adverse events occurred in pediatric as in adult populations, i.e., post-operative pain (42%), vomiting (36%), and fever (17%).

Please note Appendix VIII for the sponsor's Table 37 "Most Common Adverse Events".

Table 8

From Most Common Adverse Events ≥ 5%: Pediatric Studies (based upon Sponsor's Table 21)

Event	Levobupivacaine (ISS) N=20 n (%)	Levobupivacaine (Update) N=36 n (%)	Bupivacaine (Update) N=146 n (%)	No Treatment (ISS) N=15 n (%)
Bradycardia	1(5)	2(6)	0	0
Post-op Pain	15(75)	15 (42)	0	0
Vomiting	5 (25)	13 (36%)	5 (71)	8
At Least One AE	19 (95)	30(83)	6 (86)	13 (87)

(based upon Sponsor's Table 21, Safety Update, p.058)

Updated pharmacokinetic data obtained from pediatric studies has been submitted for review. . Analysis of this data was made by the reviewing pharmacokineticist, Suresh Doddapaneni, Ph.D. who states that, "...since full study reports have not been submitted, it is not possible to do a formal review of those studies." However, "....the data submitted did not raise any special safety concerns."

Bupivacaine Controlled Phase II/III Studies

Adverse events were pooled across all surgical anesthesia studies compared between those treated with levobupivacaine and bupivacaine. The overwhelming majority of patients were diagnosed with hypotension, which occurred with equal frequency between groups (levobupivacaine 21%, bupivacaine 23%). There were other adverse events that occurred at a two-fold greater frequency in levobupivacaine versus bupivacaine; i.e., albuminuria (3%), urinary incontinence (1.3%), urinary tract infection (1.1%); however, as can be seen, the frequency with which these adverse events occurred were < 5%.

No additional data was presented in the safety update; according to the sponsor, there were no new trends observed.

All Phase II/III Trials

The most frequently reported (≥ 5%) reported adverse events from the pooled database (phase II/III) were hypotension (30%), nausea (17%), fever, anemia (15%), postoperative pain (12%), vomiting (11%), pain, dizziness, constipation (7%), headache (6%), back pain, pruritus, urinary retention, and bradycardia (5%). The sponsor has not provided an updated "head-to-head" analysis by body system of the levobupivacaine versus bupivacaine associated adverse events. However, according to the sponsor, "No clinically relevant changes in the overall adverse event profile were observed since the original NDA submission."

The updated safety database provides no additional support for the sponsor's assertion of an improved safety profile over bupivacaine. The product was associated with qualitatively and quantitatively similar side effects commonly seen with other local anesthetics, e.g., hypotension, nausea and vomiting, urinary retention, and specifically, bupivacaine.

0.75% Levobupivacaine Phase II/III Studies

Of special concern is the highest concentration of levobupivacaine, i.e., 0.75%. This concentration of bupivacaine, (subject of box warning for bupivacaine), has been associated with cardiac arrest when accidentally injected in parturients. As previously mentioned, it is the subject of the Anesthetic and Life Support Advisory Committee meeting discussion.

The sponsor has found this concentration to also be problematic when administered to patients in clinical trials. Compared to patients in all Phase II/III studies, the patients who received the 0.75% levobupivacaine concentration were at a higher risk for experiencing at least one adverse event. Of particular interest is the finding that all of the patients who were discontinued due to an adverse event received the 0.75% levobupivacaine concentration (N=4).

Since the original NDA submission, no data have been analyzed from studies that assess the 0.75% levobupivacaine concentration.

Please note Appendix IX for the sponsor's Table 29 and 39 Comparative Adverse Events.

8.2.1 Special Safety Evaluation: Cardiovascular Safety

The clinical development program of levobupivacaine was specifically designed to evaluate the products effects on cardiovascular function. The sponsor has designed five clinical trials and one integrated analysis of four of these trials to determine and compare the effects of levobupivacaine and bupivacaine on QT dispersion and QRS intervals.

- Study 030831-EKG Analysis for a Series of Chiroscience Clinical Studies
- Study 004801-Comparison of the Cardiovascular Effects of Racemic Bupivacaine and Levobupivacaine in 14 healthy male Volunteers
- Study CS005-Double blind Randomized Controlled trial of 0.75% Levobupivacaine compared to 0.75 % Bupivacaine for Epidural Anesthesia in Patients undergoing major Abdominal Surgery
- Study 030721-Randomized Single Center Double blind Parallel Group Study to compare the Efficacy and Safety and Pharmacokinetics of 0.25% Levobupivacaine with 0.25% Bupivacaine Given as infiltration Anesthesia in Patients undergoing Elective Inguinal Hernia Repair.
- Study 030632-Double blind, Randomized, Controlled trial of 0.5% Levobupivacaine Compared to 0.5% Bupivacaine for Extradural Anesthesia in Patients Undergoing Elective Cesarean Section

8.2.1.1 STUDY 030831

Study 030831 is an integrated analysis of four separate clinical trials, (004801, Cs005, 030721 and 030632) the objective of which was to determine the effects on QT dispersion or QRS interval following exposure to levobupivacaine or bupivacaine. The hypothesis being that levobupivacaine has little effect on cardiac electrical parameters, notably QT dispersion or QRS duration.

8.2.1.2 STUDY 004801

Study 004801 was a double blind, randomized, crossover study in subjects dosed with intravenous bupivacaine or levobupivacaine to CNS symptomatology. The study was designed to compare the cardiovascular effects of racemic bupivacaine and levobupivacaine in healthy male volunteers. Dosages for which CNS symptoms were seen were 150 mg of levobupivacaine and 110 mg of bupivacaine.

QT dispersions were obtained for all 14 subjects. Other parameters included stroke index, acceleration index, ejection fraction, QT dispersion, PR interval, QRS duration, QT interval and QTc . These were compared from pre-dose to the maximum observed post-dose value. The Primary Endpoint was difference in QT dispersion from pre-dose to the maximum observed post-dose value.

The results showed that the estimate of treatment difference was -5.4 ms, which was not statistically significant (p=0.47). The secondary endpoints of PR intervals, QRS intervals, and QT intervals were also not significantly different between treatments.

Table 9. Study 004801

Parameter	Levobupivacaine (max. dose 150 mg as iv. infusion)	Bupivacaine (max. dose 10 mg as iv. infusion)
QT dispersion (mean maximum)	74.0 ± 17.8	68.1 ms ± 19.1
ΔQT dispersion †	12.2 ms ±22.9	17.7 ms ± 18.8
Est. treatment difference	-5.4 ms (NS) ‡	

† Difference in QT dispersion from pre-dose to maximum observed post-dose value
‡ p=0.47 (ANOVA) /95% CI (-21,10.2)

8.2.1.3 STUDY CS005

Study CS005 was conducted in a double blind, randomized fashion comparing 0.75% Levobupivacaine to the same dose of bupivacaine. ≥150 mg of study drug was administered depending upon whether an additional 7 ml of study drug was needed during surgery. Twenty-nine signal-averaged ECG measurements were obtained at 15 min, 30 min, 45 min 1h, 2h and 4h. The primary endpoint was the difference in QT dispersion from pre-dose to the maximum observed post-dose value. However, the QRS data were those upon which statistical analyses were performed. The results showed that the estimate of treatment difference was -0.4 ms, which was not statistically significant (p=0.76).

Table 10. Study CS005

Parameter	Levobupivacaine	Bupivacaine
QRS duration (mean median)	113.6ms ± 6.9	119.6 ms ± 22.0
Δ QRS duration †	4.2 ms ±3.7	4.5 ms ± 2.6
Est. treatment difference	-0.4 ms (NS) ‡	

† Difference in QRS duration from pre-dose to maximum observed post-dose value
‡ p=0.76 (ANOVA) /95% CI (-3.0,2.2)

8.2.1.4 STUDY 030721

Study 030721 compared 0.25% Levobupivacaine with 0.25% Bupivacaine. 150 mg of study drug was administered and 67 signal averaged ECG and QT dispersions were obtained at predose, end of surgery, and +4 hours post exposure. The Primary Endpoint was the difference in QT dispersion from pre-dose to the maximum observed post-dose value. Statistical analyses were performed on the QRS data as well. The results showed that the estimate of treatment difference was –1.0 ms, which was not statistically significant (p=0.83).

Table 11. Study 030721

Parameter	Levobupivacaine	Bupivacaine
ΔQT dispersion*	2.6 ms ± 19.0 ms	3.6 ms ±20.9 ms
Est. treatment difference	-1 ms (NS)**	
QRS duration	135 ms ± 35.3 ms	134 ms ± 36.9 ms
Δ QRS duration †	3 ms (range -72,111)	6 ms (range -47,111)
Est. treatment difference	-3 ms (NS) ‡	

*Difference in QT dispersion from pre-dose to maximum observed post-dose value

**p=0.83/95% CI (-10.9, 8.9)

† Difference in QRS duration from pre-dose to maximum observed post-dose value

‡ p=0.52 (Wilcoxon 2-sample t-test) /95% CI (-23,4)

The last study included in the meta-analysis is :

8.2.1.5 STUDY 030632

Study 030632 compared 0.5 % levobupivacaine and bupivacaine. 125 – 150 mg of study drug was administered depending upon the need for top-ups. 67 measurements of ECG and QT dispersion at predose, post-dose, and recovery were made. The primary endpoint was the difference in QT dispersion from pre-dose to the maximum observed post-dose value. (Note: Not all patients had recovery recordings).

The results showed that the estimate of treatment difference was –1.09 ms, which was not statistically significant (p=0.79). The secondary endpoints of PR intervals, QRS intervals, and QT intervals were also not significantly different between treatments.

Table 123. Study 030632

Parameter	Levobupivacaine	Bupivacaine
QT dispersion (mean median)	43.62 ms ±16.13	43.53ms ± 13.50
ΔQT dispersion †	-0.18 ms ± 20.06 ms	0.90 ms ± 11.80 ms
Est. treatment difference	-1.09 ms (NS)‡	

† Difference in QT dispersion from pre-dose to maximum observed post-dose value

‡ p=0.79(ANOVA) /95% CI (-9.25,7.08)

Additionally, **Study 012105** was a two phase analysis of cardiovascular effects of levobupivacaine when administered intravenously in an open label fashion followed by a double blind, randomized evaluation of the effects of levobupivacaine and racemic bupivacaine on myocardial depolarization and repolarization as measured by QRS duration of signal averaged EKG, and QT dispersions in healthy males. In this study, as in the previous EKG study, subjects were dosed with bupivacaine and levobupivacaine to CNS symptomatology.

The objective of this study was to compare the QT dispersion (from blinded review) and PR, QT, QTc and signal averaged QRS duration by dose of racemic- and s-bupivacaine. 30-120 mg was reached in both groups. The primary endpoints were the maximum positive change from predose using the end of infusion, 5 minute, 10 minute, 15 minute, and 30 minute time points for the QT dispersion and signal averaged QRS values for each treatment. Secondary endpoints for the same time points were PR, QT and QTc duration for each treatment.

The sponsor concedes that there are no statistically significant changes from baseline in the primary endpoints QT dispersion and QRS duration, or for the secondary endpoints changes from baseline in the PR and QT intervals between the two treatments. However, while there did appear to be a statistically significant difference between the two treatments with regard to the change from baseline in the QTc, this endpoint was chosen prospectively to be secondary in nature was just one isolated finding among many endpoints which were shown not to be statistically significant.

Dr. John P. DiMarco, Director of the Clinical Electrophysiology Laboratory and Associate Division Head, Cardiovascular Division, University of Virginia consulted with the FDA on the evaluation of the cardiovascular safety of levobupivacaine. His conclusion, "...based upon both the hemodynamic and electrocardiographic data it is difficult to be certain that there will be clinical advantages with use of levobupivacaine. It is of course difficult to compare the potential toxicity of two agents where the expected toxicity would only occur during conditions not achievable in standard clinical trials. The cardiovascular effects of levobupivacaine and bupivacaine appear to be similar with a trend favoring levobupivacaine. Based on the data I presented however, I would not feel that the trend is not conclusive enough to support a labeling claim of superiority."

8.2.2 Search Strategy

My search strategy for identifying the significant cardiovascular adverse events was to perform a "head to head" comparison of all reported cardiovascular adverse events in the levobupivacaine clinical development program comparing levobupivacaine with bupivacaine pooled across all studies. The following data was obtained from the safety database.

Table 13

Cardiovascular Adverse Events Reported in ≥ 1% of Levobupivacaine-Treated Patients: All Studies Using Bupivacaine Control

Event	Treatment Group			
	Levobupivacaine N = 445		Bupivacaine N = 391	
	N	%	N	%
Hypotension	97	22	91	23
ECG Abnormal	16	4	17	4
Bradycardia	11	3	9	2
Tachycardia	9	2	7	2
Hypertension	5	1	8	2

Clearly, there is very little difference in the percentage of cardiovascular adverse events reported between the 2 groups. According to the sponsor, only slight differences in the levobupivacaine group were noted in the updated database.

Secondly, I separated the clinical trials according to category and found the following similar results.

In the obstetric population, there again was very little evidence to support any claims of superiority. No data have been analyzed from obstetric studies since submission of the original NDA.

Table 14

All Cardiovascular Adverse Events Reported in any Treatment Group – Phase II/III Obstetrics (Update)

Event	Treatment Group			
	Levobupivacaine N = 184		Bupivacaine N = 188	
	N	%	N	%
Hypotension	60	33	71	38
Chest Pain, substernal	1	0.5	0	0
Extrasystoles	1	0.5	0	
Chest Pain,	1	0.5	3	2
Hypertension	2	1	6	3

Bradycardia	0	0	2	1
Tachycardia	2	1	2	1
Dyspnea*	0	0	2	1

In the central block population, of interest is the 8:0 incidence of bradycardia in favor of bupivacaine. However, the number of patients in each group must be taken into consideration. No data have been analyzed from central block studies since submission of the original NDA.

Table 15

All Cardiovascular Adverse Events Reported in any Treatment Group – Phase II/III Central Block (Update)

Event	Treatment Group			
	Levobupivacaine N = 109		Bupivacaine N = 57	
	N	%	N	%
Hypotension	39	36	19	33
Arrhythmia	0	1	2	1
Myocardial Ischemia	0	0	1	2
Chest Pain	1	1	0	
Hypertension	2	2	1	2
Bradycardia	8	7	0	0
Tachycardia	5	5	3	5
Pulmonary Edema*	3	3	3	5
Dyspnea*	2	2	0	1
Syncope*	0	0	1	2

*May or may not be of cardiovascular origin.

In the pain management population, again the 2 drugs behaved similarly. However, with respect to the incidence of tachycardia, bupivacaine demonstrates a 2-fold increase in cases reported. Similarly, based upon this one isolated finding one can not conclude that there is clear evidence that bupivacaine is less safe.

No data have been analyzed from pain management studies since submission of the original NDA.

Table 16

All Cardiovascular Adverse Events Reported in any Treatment Group – Phase II/III Pain Management (Update)

Event	Treatment Group			
	Levobupivacaine N = 179		Levobupivacaine + Other N = 147	
	N	%	N	%
Hypotension	111	62	116	79
Arrhythmia	1	1	2	1
Atrial Fibrillation	2	1	0	
Palpitation	1	1	0	
Heart Block	0	0	1	1
Cardiac Arrest	0	0	1	1
Angina Pectoris	1	1	0	
ECG Abnormal	1	1	1	1
Extrasystoles	1	1	2	1
Bradycardia	19	11	16	11
Tachycardia	5	3	9	6
Hypertension	5	3	6	4
Dyspnea*	4	2	11	7.5
Pulmonary Edema*	2	1	5	3
Syncope*	1	0.6	3	2
Peripheral Edema*	14	8	20	14

* May or may not be of cardiovascular origin

The analysis of the cardiovascular adverse events reported in the peripheral block studies demonstrated the same overall trend. The updated database includes 14 levobupivacaine–treated patients only; therefore, interpretation of these updated results is difficult.

Table 17

Cardiovascular Adverse Events Reported in any Treatment Group – Phase II/III Peripheral Block (UPDATE)

Event	Treatment Group									
	Levobupivacaine (Update) N=224		Levobupivacaine† (ISS) N=210		Bupivacaine† (ISS) N = 146		2% Lidocaine With Epinephrine† (ISS) N=31		Placebo† (ISS) N=31	
	N	%	N	%	N	%	N	%	N	%
Hypotension	3	1	NR		1	1	0		0	
Bradycardia	5	2	NR		7	5	0		0	
Arrhythmia	1	0.4	NR		1	1	0		0	
Extrasystoles	0		NR		2	1	0		0	
Circulatory Failure	0		NR		2	1	0		0	
ECG Abnormal	16	7	16	8	17	12	0		0	
Tachycardia	2	1	NR		2	1	0		0	
Hypertension	1	0.4	NR		1	1	0		0	
Syncope	1	0.4	NR		1	1	0		0	
Dyspnea**	1	0.4	NR		0		0		0	
Peripheral Edema	1	0.4	NR		0		0		0	

† - Only those cardiovascular adverse events occurring with a frequency 5% were reported in the original NDA, i.e., ECG abnormal.

NR – Not reported in the original NDA.

*- Occurred at a frequency of 4.8%; all numbers have been rounded to then nearest decimal point.

** - may or may not be of cardiovascular origin

Finally, in the pediatric study, when patients received either levobupivacaine or no local anesthetic at all, the cardiovascular adverse events occurred only in levobupivacaine treated group. Despite the small sample size, there is some suggestion that levobupivacaine is associated with more cardiovascular adverse events than placebo.

It is also difficult to perform a comparative analysis of the updated database, which includes a bupivacaine-controlled (N=7) and a non-comparative levobupivacaine study (total N=36).

Table 18

All Cardiovascular Adverse Events Reported in any Treatment Group - Phase II and III Pediatrics (Update)

Event	Treatment Group							
	Levobupivacaine (Update) N=36		Levobupivacaine† (ISS) N=20		Bupivacaine† (Update) N = 7		Placebo (ISS) N=15	
	N	%	N	%	N	%	N	%
Bradycardia	2	6	1	5	7	5	0	
Arrhythmia	1	3	1	5	0		0	

† There were no bupivacaine – treated patients in the original NDA

Next, I chose one cardiovascular adverse event, namely bradycardia, and gathered as much details of the surrounding episode as possible. I chose bradycardia because it occurred with a fair amount of frequency, i.e., <5%, and was associated with asystole on at least 2 separate occasions.

Severe Bradycardia with Transient Decrease in Cardiac Output
The first episode occurred in a 66 year old male with a history of essential hypertension (R_x - Atenolol) and osteoarthritis (naproxen) who was scheduled to undergo knee replacement. A T12-L1 epidural was achieved with 10 ml 0.125% levobupivacaine bolus (divided doses).

Pre-operative vital signs were significant for ECG: sinus rhythm at 55 bpm, BP145/95, and oxygen saturation of 97%. Ten minutes following study drug administration, the patients heart rate dropped to 40 bpm and BP was 95/45. He was found to be pale, nauseated and immediately thereafter - unarousable with a "flat line" ECG.

He was successfully resuscitated with ephedrine and atropine. Sensory block was said to be at T6-T7 and to subsequently rise to T2. The possibility of a high spinal was entertained.

Bradycardia with Asystole
Another episode occurred in a 46 year old female with a history of GI reflux, anemia, renal carcinoma, and asymptomatic bradycardia (pre-operative HR 50-60 bpm). Patient was scheduled to undergo a radical nephrectomy. A total of 12 ml of 0.75% levobupivacaine was administered.

The intraoperative course was significant for pneumothorax that was said to be secondary to dissection of multiple adhesions close to the diaphragm. One hour following study drug infusion in the recovery room, the patient's HR dropped to 40-60 followed shortly thereafter by the onset of asystole. The patient was resuscitated. The possibility of a vasovagal etiology for this cardiovascular instability was entertained in light of the vomiting that occurred just prior to the episode.

Bradycardia and Death

A seventy year-old male with a history of gastrointestinal disorder (R_x - ranitidine) underwent left hip surgery using 15ml of 0.75% levobupivacaine followed by an infusion of 0.125% levobupivacaine + 50 ug/hr clonidine-epidurally administered.

His preoperative ECG demonstrated a left ventricular hemiblock, HR 76, and BP 152/90. One hour following study drug administration, his HR 64, BP 100/45. The bradycardia continued for the ensuing 27 hours, with heart rates in the 50s and 60s. ECG showed a left axis deviation consistent with preoperative findings.

The patient died 11 days post treatment. In light of the temporal relationship, it is unlikely that the cause of death is attributed to levobupivacaine exposure; however, there is a strong theoretical basis for postulating a levobupivacaine-induced toxicity for which the practitioner should be cautioned. Patients who would be considered susceptible to bradycardia, or to its sequelae should be carefully chosen or at the very least, carefully prepared for levobupivacaine administration.

8.2.3 Additional Analysis and Exploration

Upon review of the data, there was sufficient suggestion of levobupivacaine – induced bradycardia to warrant an in-depth analysis of this one adverse event. In an attempt to better categorize bradycardia, I explored it selectively, with respect to drug relatedness, effects on the incidence of adverse event dropouts and ultimately, made a judgement about levobupivacaine's relatedness to the general class of intermediate local anesthetics.

Bradycardia has long been accepted as a possible consequence of local anesthetic administration, especially in the event of a high dermatomal level of blockade. If a causal relationship is found between levobupivacaine and bradycardia, i.e., typical local anesthetic side effect, than it is not unreasonable to extrapolate all other typical local anesthetic sides seen with the intermediate – acting local anesthetics, such as, hypotension, cardiorespiratory and CNS possible consequence of levobupivacaine administration for which the clinician should be cautioned.

First I examined the adverse dropouts to determine whether any of this subset of patients experienced bradycardia following levobupivacaine – exposure. Study 030475, in which patients received an epidural infusion of study drug for post-operative pain management, produced two such patients.

1. Patient 133 underwent a radical nephrectomy for renal carcinoma complicated by an intraoperative pneumothorax. While in recovery, she received a bolus dose of levobupivacaine with morphine and developed bradycardia and eventually asystole. The onset of bradycardia was said to have occurred following an episode of vomiting leading the investigators to conclude that a vasovagal etiology for the bradycardia and asystole. *Clearly bradycardia can be caused by a surge of parasympathetic output as can occur with vomiting; however, it is also equally possible that the bradycardia was secondary to a high dermatomal level and subsequent sympathetic blockade induced by levobupivacaine bolus dose administration.*
2. Patient 0040 was a 66 year old male with a history of hypertension (Rx – atenolol), dyspepsia and osteoarthritis who subsequent to receiving 10 ml of 0.75% levobupivacaine (in divided doses) experienced bradycardia, decreased cardiac output and a flat line EKG. Patient recovered and underwent an uneventful knee replacement. *This case is a clear example of drug induced cardiovascular depression. There are no other reasonable conclusions to be drawn.*

In conclusion, I concede that the incidence of bradycardia dropouts is remarkably low; however the overall incidence of bradycardia (30%) is sufficient evidence to support the conclusion that levobupivacaine when administered epidurally is capable of causing bradycardia, as is commonly seen following other local anesthetics. It is important therefore, to alert the clinician of this possibility and that the possibility for other typical local anesthetic side effects to occur following levobupivacaine administration exists.

OTHER ADVERSE EVENTS

8.2.4 Adverse Events by Age

The age category with the largest number of participants is the 14-<55 years (N=669), followed by the 55-<75 years (N=420), ≥75 years (n=131) and ≤13 years (N=20). Adverse events reported during labor and delivery were only applicable to the 14-<55 years age group, as a result there is disproportionately large number of adverse events occurring in this age category.

Bradycardia occurred most frequently in the ≥ 75 years of age group and in the levobupivacaine treatment group. The most frequently reported adverse event was pain, followed by hypotension, nausea, fever, anemia, and vomiting. Hypotension was most frequently reported in levobupivacaine + other group (79%).

The patients in the levobupivacaine + other (i.e., morphine, fentanyl or clonidine) reported the occurrence of post-operative pain most frequently and with an inverse relationship to age (see Table 23 below). However, hypotension did not demonstrate an inverse relationship to age, as outlined below:

- In the 14-<55 years of age group, the incidence of hypotension was similar between the levobupivacaine and bupivacaine groups;
- In the 55-<75 years and ≥ 75 years of age group, the incidence of hypotension was higher in the levobupivacaine group over bupivacaine group.

Adult patients (≥18 years) were similar with respect to their reporting of adverse events. No patients under the age of 18 years had serious adverse events or were discontinued from the study due to an adverse event. However, the percentage of patients under the age of 18 who experienced at least one adverse event was higher than all other age categories.

Please note Appendix X. for the sponsor's Table 38 Age–Related Adverse Events.

8.2.5 Adverse Events by Gender

The sponsor has combined data on gender with data obtained from the obstetric population. The analysis showed a slightly higher percentage of males vs. females (pregnant or non-pregnant) recording at least one adverse event. Additionally, there was at least a one and a half fold increase in males recording at least one adverse event in the levobupivacaine + other group compared to the lidocaine + epinephrine group. The percentages of pregnant females with at least one adverse event were 78.3% in the levobupivacaine group vs. 72.3% in the bupivacaine group.

With respect to the percentages of patients in the levobupivacaine + other group reporting moderate or severe adverse events that were considered to be possibly related to study drug administration, the percentage of males reporting adverse events was higher (56.1%) than the percentage of non-pregnant females (40.0%). No pregnant females were included in this study group.

The percentages of patients with serious adverse events were similar between non-pregnant females and males but highest for pregnant females; the sponsor believes this difference is due to cesarean sections being reported as serious adverse events.

Please note Appendix XI for the sponsor's Table 8.5 Gender-Related Adverse Events.

8.3 Other Safety Findings

8.3.1 Clinical Laboratory Evaluations

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

8.4 Drug-Drug Interaction

8.4.1 Interaction with Antihypertensives

The sponsor conducted an ad hoc analysis of data obtained from studies (Studies 006175 and CS 005) in which levobupivacaine or bupivacaine was given to patients currently taking one of three antihypertensives, i.e., beta-blockers, calcium channel blockers or angiotensin–converting enzyme (ACE) inhibitors. Study 006175 was a double blind, randomized, 3 limb parallel analysis of 0.5% levobupivacaine (75 mg), 0.75% levobupivacaine (111.2 mg) and 0.5% bupivacaine (75 mg) given as an epidural anesthetic to patients for elective lower limb surgery. Study CS-005 was a double blind, randomized, parallel analysis of 0.75% levobupivacaine (150 mg) and 0.75% bupivacaine (150 mg) given as an epidural anesthetic to patients for abdominal surgery.

One hundred and thirty-three (133) patients were given a study medication and 22 were either hypertensive, receiving antihypertensive medication, or receiving beta-blockers for anxiety. Of these 22 patients, 5 patients (23%) were treated with 0.5% levobupivacaine, 8 patients (36%) were treated with 0.75% levobupivacaine and 9 patients (41%) were treated with 0.5% bupivacaine. The sponsor reports that there was, "... no clear evidence of a pharmacodynamic interaction between levobupivacaine or bupivacaine and beta blocking agents or ACE inhibitors; there was possibly an interaction between the two long-acting local anesthetics and calcium channel blockers, although the numbers of patients studied preclude conclusive findings."[7]

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[7] Item 8, Vol. 1.97, p. 098

A retrospective analysis performed in over 2000 patients who received levobupivacaine or bupivacaine epidurally reportedly revealed that patients taking beta blockers were at, "no greater risk of severe hypotension than were patients not taking beta blockers."[8]

No updated data was submitted.

Please note Appendix XII for the sponsor's Table 40-42 Antihypertensives.

8.5 Summary of Potential Adverse Events Considered Related to Study Drug

Levobupivacaine appears to have a similar safety profile to other local anesthetics, i.e., hypotension, nausea and vomiting, dizziness, delayed delivery, fetal distress. However, of interest is the occurrence of fever and anemia, which is not typical of local anesthetics. Fever occurred in 5.8% of patients in the levobupivacaine group and in 6.9% of the bupivacaine-exposed population. A similar frequency was seen in those reporting anemia, i.e., 11.0% levobupivacaine and 9.5% bupivacaine.

It is likely that these events demonstrate what is typically seen in patients in the first 72 hours following an operation. Possible explanations for post-operative hyperthermia include the following: mobilization of existing infection by the surgical procedure, atelectasis, and unrecognized intraoperative aspiration. Many drugs have been implicated, as well, including atropine, muscarinic neuromuscular blocking agents, halogenated volatile agents (i.e., malignant hyperthermia) and transfusion reactions.

Please note Appendix XIII for the sponsor's Table 43. Adverse Events Reported in ≥ 1% of Levobupivacaine – Treated Patients

[8] Item 8, Vol. 1.97, p. 096

9.0 CONCLUSIONS

Based upon review of the data submitted, levobupivacaine appears to be reasonably safe when used as recommended. However, with respect to claims of improve cardiovascular safety over that of bupivacaine, the sponsor has not provided sufficient evidence to prove this indecisively.

Additionally, the sponsor has demonstrated the efficacy of levobupivacaine in the production of surgical anesthesia and pain management.

10.0 RECOMMENDATIONS

In the opinion of this reviewer, NDA 20-997 should be approved.

Monica Roberts, M.D.
Division of Anesthetics, Critical Care and Addiction Drug Products
February 25, 1999

cc: NDA-20-997
HFD-170 File
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McCormick
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REVIEW and EVALUATION of CLINICAL DATA

NDA:	20-997
SPONSOR:	DARWIN DISCOVERY LTD (PAREXEL)
DRUG:	CHIROCAINE (LEVOBUPIVACAINE) INJ.
PROPOSED INDICATION:	SURGICAL ANESTHESIA/ PAIN CONTROL
CLINICAL REVIEWER:	MONICA L. ROBERTS, M.D.
ORIGINAL RECEIPT DATE:	April 29, 1998 August 27, 1998
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MATERIALS RECEIVED:	NDA- 20-997 Amendment to NDA: 120 Day Safety Update
PROJECT MANAGER:	SUSMITA SAMANTA, MD

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