

Table 6.

Table 2 Patient Disposition

Patients	Levobupivacaine/ Fentanyl N (%)	Levobupivacaine N (%)	Fentanyl N (%)	All Patients N (%)
Patients Randomized	22 (100)	23 (100)	23 (100)	68 (100)
Withdrawn Prior to Anesthesia (Not Treated)	0	1 (4.3)	1 (4.3)	2 (2.9)
Received Levobupivacaine for Anesthesia (Safety Population)	22 (100)	22 (95.7)	22 (95.7)	66 (97.1)
Received Randomized Study Drug (ITT Population) for Analgesia	21 (95.5)	22 (95.7)	22 (95.7)	65 (95.6)
Per-Protocol Evaluable	18 (81.8)	21 (91.3)	21 (91.3)	60 (88.2)
Non-Protocol Evaluable	3 (13.6)	1 (4.3)	1 (4.3)	5 (7.4)
Discontinued	5 (22.7)	11 (47.8)	12 (52.2)	28 (41.2)
Completed	17 (77.3)	12 (52.2)	11 (47.8)	40 (58.8)

Abstracted from Statistical Table 1.

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

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Primary Efficacy Analyses:

The following table copied from Dr. Roberts' Table 108, page 200 of her review, summarizes the results for the primary outcome variables:

Table 7.

Table 4 Time (Minutes) to First Request for Rescue Analgesia: Intent-to-Treat Population

Time to first request for rescue analgesia (min)	Levobupivacaine/ Fentanyl	Levobupivacaine	Fentanyl
Percentile			
25%	433.0	359.0	341.0
50%	535.0	448.0	416.0
75%	1000.0	495.0	479.0
Number of censored observations	5	1	1
Mean ^{1,2}	603.05	421.50	420.45

¹ Arithmetic Mean. ² If additional dose was not requested during the 24-hour period, the time of the first request for rescue medication was censored at the completion time of the study drug administration in the 24-hour post-operative period. Means calculated using censored data are negatively biased. Due to differential group censoring, the combination group has the greatest negative bias and the levobupivacaine treatment has the least negative bias.

Pairwise Comparisons:	p - value
Combination versus fentanyl	0.007
Levobupivacaine versus fentanyl	0.679
Combination versus levobupivacaine	0.006

Abstracted from Statistical Table 7.1.

The combination group had a statistically significant treatment effect when compared to the fentanyl only group ($p = 0.007$) and to the levobupivacaine only group ($p = 0.006$). The median time to analgesic request in the levobupivacaine/fentanyl combination group was 8.9 hours, compared with 7.5 hours for the levobupivacaine only group and 6.9 hours for the fentanyl only group.

Secondary Efficacy Measures:

Proportion of Patients Who Did or Did Not Request Rescue Analgesia:

For the ITT population, 2/21 (9.5%) patients in the combination treatment group did not self administer rescue medication during the 24 hour period, compared with 1/22 (4.5%) patients in the levobupivacaine only group and 0 patients in the fentanyl group. None of the pairwise comparisons resulted in statistically significant treatment differences ($p = 0.386, 0.126$ and 0.355 for the combination vs. levobupivacaine, combination vs.

fentanyl, and levobupivacaine vs. fentanyl comparisons, respectively).

Amount of Rescue Medication Administered:

The volume of rescue medication used was compared across the treatment groups at 6, 12, 18 and 24 hours. There were no statistically significant differences between any treatment groups at any time point. [see Dr. Roberts' Table 110, page 202 of her review.]

Proportion of Patients Requiring Femoral Nerve Block

For the ITT population, 3/21 (14.3%) combination treatment patients, 4/21 (18.2%) levobupivacaine only patients, and 5/21 (22.7%) fentanyl only patients required a femoral nerve block during the 24 hour period. There were no statistically significant treatment differences with $p = 0.298$, 0.414 and 0.789 , for the combination, levobupivacaine only and fentanyl only groups, respectively.

Extent of Motor Block:

Motor block assessments were performed at 6, 12, 18 and 24 hours post-operatively or until the patient had no lingering paralysis. By 12 hours most patients had regained full movement of their lower limbs. Patients treated with levobupivacaine alone had consistently higher average Bromage score than the other two treatment groups. The three groups were different significantly at 6 hours with $p=0.013$ by ANOVA. In the pairwise comparison at 6 hour, patients treated with levobupivacaine and fentanyl combination had no statistically significant difference from the patients treated with fentanyl alone ($p=0.85$). The only significant pairwise comparison was between levobupivacaine alone and fentanyl alone, with the levobupivacaine group having a significantly higher mean score (1.1 vs. 0.2 with $p=0.004$). The p -value was significant with adjustment for 3 pairwise comparisons. The combination treatment had a slightly higher (but not statistically significant) mean than either the levobupivacaine alone or the fentanyl alone group.

Patient VAS at Rest and When Coughing:

VAS scores were obtained 6, 12, 18 and 24 hours post-surgery. At rest, the combination group had a statistically significantly lower score than the fentanyl only group at 6 and 12 hours ($p = 0.022$ and 0.002 , respectively). While coughing, the combination group had a lower VAS score than the fentanyl only group at 6 hours and 12 hours ($p = 0.036$ and 0.001 , respectively). There were no significant treatment differences between the three groups at any other time points.

Global VAS by Patient and Investigator:

The overall patient assessment means were 1.66, 2.81, and 3.82 on the VAS for the combination, levobupivacaine only, and fentanyl only groups, respectively. The

treatment difference between the combination and the fentanyl only groups was statistically significantly ($p = 0.007$). The combination group (adjusted mean = 1.35) also had statistically significantly lower overall investigator pain assessment scores than the fentanyl only group (adjusted mean = 3.54), with $p = 0.005$.

Comments:

The time to first request for rescue medication was statistically significantly longer for the combination treatment than either of the other two treatments. However, in the secondary outcome measures there were no consistent, statistically significant differences between the groups for proportion of patients requesting rescue medication, amount of rescue medication administered, proportion of patients requiring femoral nerve block, and extent of motor block. Pain relief did seem to be greater with the combination treatment, but not consistently.

STUDY 030742:

This was a randomized, double-blind, parallel group, single center study comparing 0.125% levobupivacaine, 0.125% levobupivacaine plus clonidine, and clonidine alone, administered as a continuous epidural infusion for post-operative pain in patients undergoing elective hip replacement surgery.

Patients were randomized 1:1:1 to one of the three treatment arms: either 0.125% levobupivacaine, 0.125% levobupivacaine with 50 mcg/hr clonidine, or 50 mcg/hr clonidine. The patients were pretreated with temazepam 20 mg and ranitidine 150 mg. Prior to surgery, patients were administered 0.75% levobupivacaine via an epidural catheter to a maximum of 15 mL, after a test dose of 3 mL of 2% lidocaine with epinephrine. If, after 30 minutes, an appropriate block for surgery had not been attained, additional 1 mL boluses of study drug were administered up to 5 mL. If, after another 15 minutes, the level of block was not adequate, the patient was withdrawn from the study. Three hours after the bolus injection, patients were started on study drug infused at 6 mL/hr for 24 hours. Propofol was administered intraoperatively as needed. Morphine was available via PCA pump as rescue medication during the 24 hour post-operative infusion period.

The primary measure of efficacy was the time total dose of morphine delivered via the PCA pump during the 24 hour post-operative infusion period.

Secondary efficacy measures included:

1. Time to first request for analgesia during the 24 hour period following completion of the epidural injection;
2. Number of requests for analgesia;

Results:

A total of 98 patients were randomized. Of the 98 patients, 96 received study medication and were included in the safety population. Two patients (one randomized to the levobupivacaine treatment group and the other to the clonidine treatment group) were excluded from the safety population prior to receiving 0.75% levobupivacaine as presurgical anesthesia. The reason given was "technical failure." Six patients (four clonidine treated and two combination treated) were excluded from the ITT population because of technical failure, insufficient block, requiring general anesthesia during surgery, or inability to complete assessments; none of these patients received the complete study infusion. Four patients (three levobupivacaine treated and one clonidine treated) were excluded from the PP population based on 'protocol violations.' The following table copied from Dr. Roberts' Table 114, page 217 of her review, summarizes the patient disposition:

Table 8.

Summary of formation of populations
by treatment group
Total population

Evaluation group	Levobupivacaine (n=31)	Levobupivacaine plus Clonidine (n=32)	Clonidine (n=35)
Total population	31 (100.0%)	32 (100.0%)	35 (100.0%)
Safety population	30 (96.8%)	32 (100.0%)	34 (97.1%)
Intent-to-treat population	30 (96.8%)	30 (93.8%)	30 (85.7%)
Per-protocol population	27 (87.1%)	30 (93.8%)	29 (82.9%)

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

Primary Efficacy Analyses:

The following table copied from Dr. Roberts' Table 116, page 221 of her review, summarizes the results for the primary outcome variables:

Table 9.

TABLE 14

LEVOBUPIVACAINE - 030742

Summary and analysis of total dose of morphine
by treatment group
Intent-to-treat population

Variable		Levobupivacaine (n=30)	Levobupivacaine plus Clonidine (n=30)	Clonidine (n=30)
Morphine requirements (mg)	mean	36.5	13.9	22.6
	sd	23.7	17.3	12.8
	median	36	7	21
	minimum	4	0	0
	maximum	85	60	45
	n	30	30	30
Statistical assessments				
Wilcoxon two-sample test :		p-value	median estimate of treatment differences	95% C.I.s
Levobupivacaine v Levobupivacaine plus Clonidine		<0.001	23 mg	(9, 36)
Levobupivacaine plus Clonidine v Clonidine		0.004	-12 mg	(-18, -3)
Levobupivacaine v Clonidine		0.022	13 mg	(2, 26)

NS: patients with missing doses of morphine have been assumed to have 0mg administered only when the patient did not request morphine

Pair-wise differences between the treatment groups have been estimated as 'Levobupivacaine - Levobupivacaine plus Clonidine', 'Levobupivacaine plus Clonidine - Clonidine' and 'Levobupivacaine - Clonidine'.

For the ITT population, the median total dose of morphine administered was lowest for the levobupivacaine plus clonidine treatment group (7 mg in 24 hours). The difference was statistically significant between the combination group and the levobupivacaine group at -23 mg with $p < 0.001$. It was also statistically significantly lower than the clonidine group at -12 mg with $p = 0.004$. The levobupivacaine group had a median dose larger than the clonidine group by 13 mg. This difference was not statistically significant with $p = 0.022$ when adjustment is made for multiple comparisons with a required p value of 0.017. Similar results were seen with the PP population.

Secondary Efficacy Measures:

Time to First Request for Morphine via the PCA Pump:

For the ITT population, the median survival time to the first request for analgesia was longest for the combination treatment group (12.49 hrs including censored patients; 9.86 not including censored patients). It was longer than either the levobupivacaine group (2.85 hrs including or excluding censored patients) or the clonidine group (5.88 including censored patients; 5.83 not including censored patients). Comparisons between the groups found statistically significant treatment differences in all comparisons: $p < 0.001$ for the combination group vs. the clonidine group; $p = 0.005$ for the combination group vs. the levobupivacaine group; and, $p = 0.01$ for the levobupivacaine group vs. the clonidine group.

Number of Requests for Analgesia via the PCA Pump:

For the ITT population, the median number of requests for analgesia was 9 for the combination treatment group, 28 for the clonidine only treatment group, and 55 for the levobupivacaine only treatment group. Comparisons between the groups found statistically significant treatment differences for the combination group vs. the clonidine group ($p = 0.012$) and the combination group vs. the levobupivacaine group ($p < 0.001$). The difference between the levobupivacaine group and the clonidine group was not statistically significant ($p = 0.13$).

The following three secondary outcome measures were not included in the protocol:

Visual Analogue Pain Scale:

No formal statistical analyses were presented. In general, the three treatment groups had the same pattern of median VAS scores over time. Some variation was noted, but is of unclear clinical significance.

Height of Sensory Block:

No formal statistical analyses were presented. The combination group consistently had the highest median value of height of sensory block at the upper left and right dermatomes at all assessments after 4 hours. The clonidine group consistently had the highest median value of height of sensory block at the upper left and right dermatomes before 4 hours, but the lowest median values for both upper and lower dermatomes at all assessments after 10 hours.

Motor Block:

The majority of the patients in the combination treatment group and the clonidine only treatment group, and just under half of the patients in the levobupivacaine only treatment

group, attained the maximum grade of motor block. The levobupivacaine group had the largest number of patients who attained the lowest grade of motor block. None of the pairwise comparisons between the treatment groups found a statistically significant treatment effect.

Comments:

The total dose of morphine administered during the post-operative assessment period was statistically significantly lower for the combination treatment group compared to either the levobupivacaine only or clonidine only treatment group. Supportive results were found in the analyses of the secondary efficacy outcomes, time to first request for rescue medication and number of requests for rescue medication.

PERIPHERAL BLOCK STUDIES:

STUDY 030428:

This was a randomized, double-blind, parallel group, single center study comparing 0.25% levobupivacaine with 0.25% bupivacaine, administered as infiltration anesthesia in patients undergoing elective inguinal hernia repair.

Patients were randomized to one of two treatment arms: either 0.25% levobupivacaine or 0.25% bupivacaine. A total of 50 mL of study drug was used to infiltrate the skin and subcutaneous tissue of the area to be incised. An additional 10 mL maximum of study drug was allowed for infiltrating the wound perioperatively. Eight milliliters of study drug was then administered intracutaneously along the line of incision, followed by 12 mL into the deeper layers under the incision. Following the incision, an additional 20 mL was administered subfascially, near the pubic bone and around the cord at the deep inguinal ring. The remaining 10 mL was administered, as needed, during the dissection or at the latest of the muscle layers during the suturing of the mesh to the conjoined tendon. If, thereafter, any additional analgesia was needed, a maximum of 10 mL was allowed.

Patients were prescribed ibuprofen 600 mg TID for 4 days post-surgery.

The primary measure of efficacy was the randomized area under the VAS vs. time curve over all available assessments. Patients completed the VAS, measuring their pain at 1, 2, 3, 4, 8, 12, 24, 36 and 48 hours post-injection. These assessments were made while the patients were supine, rising from the supine to a sitting position, and while walking.

Secondary efficacy measures included:

1. VAS for satisfaction with the anesthetic;

2. Global verbal rating scale of pain experienced during surgery;
3. Normalized dosage of relief medication;
4. Time to first dose of relief medication;
5. Normalized area under supine VAS for post-operative pain vs. time curve up to first request for relief medication;
6. Normalized area under lying to sitting VAS for post-operative pain vs. time curve up to first request for relief medication;
7. Normalized area under walking VAS for post-operative pain vs. time curve up to first request for relief medication;
8. Number of relief medications taken;

Results:

A total of 67 patients were randomized. Of the 67 patients, 66 received study medication and were included in the safety population. One patient (randomized to the bupivacaine treatment group) was excluded from the safety population prior to study drug administration because he did not have a hernia. All 66 patients were included in the ITT population as well. Ten patients from the levobupivacaine group and 11 from the bupivacaine group were excluded from the PP population based on 'protocol violations.' These violations included not having a hernia, having a recurrent hernia, and, the large majority, receiving prohibited medications during or after surgery.

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

Primary Efficacy Analyses:

For the ITT population, the mean normalized area under the 'supine' VAS curve was slightly lower in the bupivacaine group (10.69 mm) than in the levobupivacaine group (12.51 mm). No statistically significant difference was detected between the treatments ($p = 0.63$) after adjusting for the normalized dosage of relief medication. The results for the PP population were similar.

The mean normalized area under the 'lying to sitting' VAS curve was slightly lower in the bupivacaine group (16.46 mm) than in the levobupivacaine group (16.72 mm). The difference was not statistically significant ($p = 0.70$). The mean normalized area under the 'walking' VAS curve was greater in the bupivacaine group (16.95 mm) than in the levobupivacaine group (13.89 mm). The difference was not statistically significant ($p = 0.06$).

For the PP population, the results were similar for the 'supine' and 'lying to sitting' analyses. For the area under the 'walking' VAS versus time curve, the levobupivacaine group had a significantly smaller AUC than the bupivacaine group ($p = 0.019$).

Secondary Efficacy Measures:

VAS of Satisfaction with the Anesthetic:

For the ITT population, the mean VAS score was 72.9 mm in the levobupivacaine group and 80.0 mm in the bupivacaine group. The difference was not statistically significant ($p = 0.17$). Results were similar for the PP population.

Global Verbal Rating Scale of Pain Experienced During Surgery:

For the ITT population, most patients reported slight to moderate pain (84.8% of the levobupivacaine patients and 87.9% of the bupivacaine patients). More patients in the levobupivacaine group reported moderate or severe pain during surgery than in the bupivacaine group. A logit regression model with proportional odds was used. The proportional odds assumption was tested and not rejected. The odds ratio was not statistically significant ($p = 0.17$). Results for the PP population were similar.

Normalized Dosage of Relief Medication:

For the ITT population, the normalized dosage of relief medication was 50.44 mg/hr in the levobupivacaine group and 50.53 mg/hr in the bupivacaine group. The median difference was 0.04 mg/hr which was not statistically significant ($p = 0.55$). Results were similar for the PP population.

Time to First Dose of Relief Medication:

Eight patients in the ITT population (2 levobupivacaine treated and 6 bupivacaine treated) did not take any relief medication and were considered censored observations. The average time to first dose of relief medication including the censored observations was 11.22 hrs in the levobupivacaine group and 14.67 hrs in the bupivacaine group. The average time to first dose of relief medication excluding the censored observations was 8.84 hrs in the levobupivacaine group and 7.26 hrs in the bupivacaine group. The difference was not statistically significant ($p = 0.45$). Results for the PP population were similar.

Normalized Area Under Supine VAS for Post-Operative Pain vs. Time Curve Up to the First Request for Relief Medication:

For the ITT population, the normalized AUC was 5.52 mm in the levobupivacaine group and 7.04 mm in the bupivacaine group. The difference was not statistically significant ($p = 0.27$). The results for the PP population were similar.

Normalized Area Under Lying to Sitting VAS for Post-Operative Pain vs. Time Curve Up to the First Request for Relief Medication:

For the ITT population, the normalized AUC was 7.13 mm in the levobupivacaine group and 8.20 mm in the bupivacaine group. The difference was not statistically significant ($p = 0.42$). Results for the PP population were similar.

Normalized Area Under Walking VAS for Post-Operative Pain vs. Time Curve Up to the First Request for Relief Medication:

For the ITT population, the normalized AUC was 6.81 mm in the levobupivacaine group and 9.62 mm in the bupivacaine group. The difference was not statistically significant ($p = 0.10$). Results for the PP population were similar.

Number of Relief Medications Taken:

The normalized number of relief medications taken was 0.102/hr in the levobupivacaine group and 0.088/hr in the bupivacaine group. The difference was not statistically significant ($p = 0.42$).

Comments:

There was no statistically significant difference in the mean area under the defined VAS curves between the study groups. There were also no statistically significant differences between the groups in any of the secondary efficacy measures.

STUDY 030721:

This was a randomized, double-blind, parallel group, single center study comparing 0.25% levobupivacaine with 0.25% bupivacaine, administered as infiltration anesthesia in patients undergoing elective inguinal hernia repair.

Patients were randomized to one of two treatment arms: either 0.25% levobupivacaine or 0.25% bupivacaine. A total of 50 mL of study drug was used to infiltrate the skin and subcutaneous tissue of the area to be incised. An additional 10 mL maximum of study drug was allowed for infiltrating the wound perioperatively. Eight milliliters of study drug was then administered intracutaneously along the line of incision, followed by 12 mL into the deeper layers under the incision. Following the incision, an additional 20 mL was administered subfascially, near the pubic bone and around the cord at the deep inguinal ring. The remaining 10 mL was administered, as needed, during the dissection or at the latest of the muscle layers during the suturing of the mesh to the conjoined tendon. If, thereafter, any additional analgesia was needed, a maximum of 10 mL was allowed.

Patients were prescribed ibuprofen 600 mg TID for 4 days post-surgery.

The primary measure of efficacy was the randomized area under the VAS vs. time curve over all available assessments. Patients completed the VAS measuring their pain at 1, 2, 3, 4, 5, 6, 8, 12, 24, 36 and 48 hours post-injection. These assessments were made while the patients were supine, rising from the supine to a sitting position, and while walking.

Secondary efficacy measures included:

1. VAS for satisfaction with the anesthetic;
2. Global verbal rating scale of pain experienced during surgery;
3. Normalized dosage of relief medication;
4. Time to first dose of relief medication;

Results:

A total of 69 patients were randomized. All 69 received study medication and were included in the safety population. All 69 patients were included in the ITT population as well. Five patients from the levobupivacaine group and 4 from the bupivacaine group were excluded from the PP population based on 'protocol-violations.' These violations included having a recurrent hernia and receiving prohibited medications during or after surgery.

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

Primary Efficacy Analyses:

For the ITT population, the mean normalized area under the 'supine' VAS curve was slightly lower in the levobupivacaine group (7.86 mm) than in the bupivacaine group (8.01 mm). No statistically significant difference was detected between the treatments ($p = 1.00$) after adjusting for the normalized dosage of relief medication. The results for the PP population were similar.

The mean normalized area under the 'lying to sitting' VAS curve was slightly higher in the levobupivacaine group (17.57 mm) than in the bupivacaine group (16.12 mm). The difference was not statistically significant ($p = 0.71$). The mean normalized area under the 'walking' VAS curve was greater in the levobupivacaine group (14.41 mm) than in the bupivacaine group (12.88 mm). The difference was not statistically significant ($p = 0.74$).

For the PP population, the results were similar for all three analyses.

Secondary Efficacy Measures:

VAS of Satisfaction with the Anesthetic:

For the ITT population, the mean VAS score was 87.09 mm in the levobupivacaine group and 87.65 mm in the bupivacaine group. The difference was not statistically significant ($p = 0.91$). Results were similar for the PP population.

Global Verbal Rating Scale of Pain Experienced During Surgery:

For the ITT population, most patients reported nil to slight pain. Fewer patients in the levobupivacaine group (2, 5.7%) reported moderate pain during surgery than in the bupivacaine group (6, 17.6%). One patient in each group reported severe pain during surgery. The sponsor compared the percentage of patients experiencing nil pain (34.3% of levobupivacaine patients; 41.2% of bupivacaine patients) and found that the treatment difference was not statistically significant ($p = 0.56$). Results for the PP population were similar.

Normalized Dosage of Relief Medication:

For the ITT population, the normalized dosage of relief medication was 52.8 mg/hr in the levobupivacaine group and 43.2 mg/hr in the bupivacaine group. The difference was 12.21 mg/hr which was not statistically significant ($p = 0.11$). Results for the PP population resulted in a p-value of 0.041, suggesting that the PP levobupivacaine patients may have taken more relief medication than the PP bupivacaine patients.

Time to First Dose of Relief Medication:

Eight patients in the ITT population (1 levobupivacaine treated and 4 bupivacaine treated) did not take any relief medication and were considered censored observations. The average time to first dose of relief medication including the censored observations was 9.33 hrs in the levobupivacaine group and 10.22 hrs in the bupivacaine group. The average time to first dose of relief medication excluding the censored observations was 9.33 hrs in the levobupivacaine group and 9.10 hrs in the bupivacaine group. The difference was not statistically significant ($p = 0.385$). Results for the PP population were similar.

Comments:

There was no statistically significant difference in the mean area under the defined VAS curves between the study groups. There were also no statistically significant differences between the groups in any of the secondary efficacy measures, with the exception of a secondary analysis on the PP population which suggested that the levobupivacaine patients may have taken more relief medication than the bupivacaine patients.



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MEMORANDUM

DATE: December 29, 1998

TO: Members of the Anesthetics and Life Support Advisory Committee

FROM: Cynthia G. McCormick, MD, Director /S/
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation III, CDER, FDA

RE: ALSAC Meeting, January 12, 1999
Levobupivacaine Safety

Members of the Division and Anesthetics and Analgesics Review Team look forward to the upcoming meeting of the ALSAC, at which time we seek your advice on the labeling for Levobupivacaine, the pure s-enantiomer of bupivacaine. The specific questions for the committee relate to the cardiovascular profile of the product, what the sponsor has undertaken to properly characterize it, and what claims should be approved for the label of this new product.

The meeting package will contain the following documents:

- Supervisory reviews of Efficacy, Safety and Statistics,
- Toxicology Summary of the cardiovascular effects of levobupivacaine
- Consultation by John DiMarco, MD, Director of the Clinical Electrophysiology Lab and Associate Division Head, Cardiovascular Division, University of Virginia
- ALSAC Meeting transcripts dated March 24, 1997
- Guidance on Local and Regional Anesthetics (1986)
- Proposed labeling for Levobupivacaine

In addition to these documents, the October 1983 ALSAC Transcripts (discussion of the cardiotoxicity of bupivacaine), the report of the subcommittee on cardiotoxicity of anesthetics, current bupivacaine labeling, 1996 ALSAC Transcripts (discussion of the same issues surrounding the approval of Ropivacaine), the labeling, the safety review,

and the reviews of cardiotoxicity of that product will be made available to you if you would like to read them as background.

The Sponsor has made a genuine effort to evaluate this product in accordance with established standards and requests of the advisory committee. While not all studies have been completed, the sponsor, in having submitted the NDA for levobupivacaine at this time, is of the opinion that the safety profile of this product has been adequately demonstrated. The review staff has no questions regarding the approvability of this product. Specific claims in the label remain the only issues left to resolve.

APPEARS THIS WAY
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FDA CENTER FOR DRUG EVALUATION AND RESEARCH
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MEMORANDUM

DATE: December 29, 1998

TO: NDA #20-997

FROM: Cynthia McCormick, MD, Director, */S/*
Division of Anesthetics, Critical Care and Addiction Drug
Products
ODE III, CDER, HFD-170

RE: Levobupivacaine Safety—supervisory review

Background

Levobupivacaine is a long acting local anesthetic agent and the pure *s*-enantiomer of bupivacaine approved 1972. Shortly after its approval, bupivacaine was associated with reports of unresuscitatable cardiac arrest due to inadvertent intravascular injection, usually during obstetrical epidural anesthesia. After relabeling bupivacaine to include a Box Warning regarding appropriate use of bupivacaine in obstetrical anesthesia, this problem has largely resolved.

In 1983 after deliberating about the cardiovascular toxicity of bupivacaine the Anesthetics and Life Support Advisory Committee (ALSAC) made a recommendation to the FDA to undertake to assess each new local anesthetic product for very specific actions and mechanisms of action as well as specific mechanisms of toxicity. This resulted in a guidance which was published approximately two years later which stated that any agent that came on the market should be studied

- to determine the dose required for effective anesthesia (that there should be a determination of blood levels following effective block in animal models and human subjects)
- to determine the doses and blood levels that would cause cardiovascular and CNS toxicity following IV infusion and multiple bolus injections;

- to determine the arrhythmogenic potential in model species, both in large and in small animal models and the electrophysiologic mechanisms in isolated tissue preparations (toxicity studies should be carried out in both pregnant and non pregnant animals¹) and
- to determine the nature of the ability to resuscitate and the kinds of agents which would be needed.

The pure s-enantiomer of bupivacaine, the active ingredient in Chirocaine, was developed as an alternative to bupivacaine as animal studies suggested that it was less cardiotoxic than the currently approved racemic product and therefore would have a superior safety profile with what was hoped would be similar efficacy. The sponsor has suggested specific language in the package insert which distinguishes its purported safety profile from that of bupivacaine, one of which is the Box Warning. The bases for these differences must be understood in terms of the comparative clinical data that are submitted to support them.

This memorandum will serve as a supervisory review and overview of the safety portion of NDA #20-997, levobupivacaine (Chirocaine). The materials considered in this review included the ISS and 4-Month Safety Update, the primary review of safety performed by Dr. Roberts, the statistical review of the same materials, the toxicology summary of preclinical data, the ALSAC Meeting transcripts from October 4-5, 1983 and March 24, 1997, guidance on regional anesthetics and the cardiovascular consultation of Dr. John DiMarco. In addition to these the 1996 ALSAC Meeting which considered the same issues surrounding the approval of Ropivacaine, the labeling, and the safety review of that product were considered.

Some of the critical preclinical studies pertinent to the cardiovascular safety of this product have not yet been completed or begun. The product's labeling will be brought for consideration before ALSAC on January 12, 1999. The committee will be asked to consider the materials that are completed and which are currently before the FDA. The committee will be asked also to consider whether the remaining studies are necessary, and whether there is sufficient information to make a decision about the proposed labeling for this product. The committee may decide that there are sufficient grounds on which to remove the Box Warning or to approve portions of the draft labeling as submitted. It may, alternatively, consider whether this product should be labeled in a manner similar to the racemic product until the investigations that were requested are completed. The studies that were requested during development will be found in the ALSAC transcripts of March 24, 1997.

¹ This was based on the observation that pregnant patients who had received Bupivacaine for epidural anesthesia appeared to be much more sensitive to the toxicity of the drug. This was confirmed by experimental preparations.

Overview of Clinical Safety

The evaluation of the human safety of this product was based on a total exposure of 1439 patients and subjects in 27 studies. There were in addition 391 active-controlled patients who received corresponding doses of bupivacaine in phase II/III studies, 31 who received lidocaine and epinephrine and 47 who received placebo. As a background for understanding the adverse event data reported in this NDA, the following groupings of trials using anesthesia for a variety of surgical, obstetrical and analgesic procedures were done for clinically meaningful pooling.

Phase I

- **Two Pharmacokinetics Studies**
- **Four Pharmacodynamics Studies (CNS, cardiovascular/electrophysiologic and peripheral N. endpoints)**

Phase II/III

Obstetrical Studies

- **Four Obstetrical Anesthesia Studies (C-section and Epidural Analgesia for Labor and Delivery).** These studies compared 0.07-0.5% levobupivacaine with bupivacaine. Baseline comparability was established with regard to proportion of patients who underwent C-section

Central Block Studies

- **Four Central Block Studies (Pain management for postoperative orthopedic and abdominal surgery).** These were epidural and spinal (open label) anesthesia for intraoperative and postoperative pain control. Doses administered intraoperatively were 75-150 mg epidurally and 15 mg spinally (0.5-0.75% levobupivacaine or bupivacaine). The infusion rates were 4-10 ml/hr of 0.0625% -0.125% levobupivacaine or bupivacaine. In addition three postoperative epidural infusion studies included the co-administration of a narcotic analgesic (classified as levo + other).
- **Three Central Block Studies (Anesthesia for lower limb and major abdominal surgery (epidural) and lower limb surgery (subarachnoid injection)).** These were double blind studies of epidural and subarachnoid administration of doses of levobupivacaine ranging from 75 mg (0.5%) to 112.5 mg (0.75%) or bupivacaine 75 mg (0.5%) to 150 mg (0.75%) for epidural administration and 15 mg (0.5%) levobupivacaine for subarachnoid administration in uncontrolled fashion.

Peripheral Block Studies

- **Seven Peripheral Block Studies: (Infiltration nerve block, brachial plexus block, peribulbar block and inferior alveolar nerve block).** In these studies a maximum dose of 150 mg and a maximum concentration of 0.75% was administered. Patients in the inferior alveolar nerve block study received 2% lidocaine with epinephrine vs. 0.75% levobupivacaine.

Pediatrics

- **Three Pediatric Studies: (ilio-inguinal nerve block and caudal epidural).** The first pediatric study, for which a completed report and adverse event

data are available is an open label study in which patients received concentrations of 0.0625%-0.126% levobupivacaine or 0.0625% levobupivacaine plus fentanyl. The second pediatric study compared levobupivacaine with bupivacaine as a caudal epidural block for anesthesia during surgery at concentrations of 0.25%. The third study has not yet contributed adverse event data to the safety database.

Other

- **One Special Analysis-Study** (integrated cardiovascular safety across four studies); Cardiovascular (EKG) endpoints were measured in patients receiving concentrations of levo bupivacaine and bupivacaine ranging from 0.25 to 0.75% and in two studies in normal volunteers, administered to onset of CNS toxicity. Doses at which CNS symptoms occurred were not statistically significant between treatment groups.

Deaths

As Dr. Roberts has pointed out in her Review of Safety, there was only one death in the levobupivacaine experience which appeared to have no direct relationship to levobupivacaine. The patient experienced a sudden fatal collapse, thought to be a myocardial infarction, however this was not confirmed. He had received levobupivacaine 11 days before the event. Pre and post-operative EKGs demonstrated left axis deviation only.

Serious Adverse Events

Sixty levobupivacaine-treated patients were reported as having serious adverse events during clinical trials with levobupivacaine and during phase II/III studies only.

In assessing the serious adverse events in the obstetrical anesthesia studies, many of the reported events included failure to progress in labor and fetal bradycardia and occurred with similar to or slightly less frequency in the bupivacaine controls and were not unexpected.

In the central nerve block group, complications of surgery such as sepsis, leaking anastomosis, ileus, ARDS, pulmonary embolism and other complications of surgery were noted.

In the postoperative pain management studies, the complications were more serious, and it would appear that the patients were more ill. There were some expected complications of surgery such as fever, pulmonary embolism, chest pain, DVT, abdominal abscess, ileus, and infection. However, in addition more serious adverse events were reported which were in some cases possibly related to drug, including asystole (209.75 mg), apnea (two patients 165 mg and 105 mg) and bradycardia (255 mg) with transient decrease in cardiac output. One patient was reported as having had a suspected IV injection and developed CNS side effects. The patients in these studies had a higher incidence of cardiovascular side effects and withdrawals due to adverse events

from all groups than in any of the other studies. These studies did not have a control group, however, so that the incidence of AEs had no comparator.

In the peripheral nerve studies there was one patient who experienced a drop in blood pressure (144.5 mg), a second with bradycardia (125 mg), and one who developed confusion (37.5 mg). In each of these cases the patients' adverse event resolved.

Withdrawals due to Adverse Events

One patient withdrew from a Phase I study due to facial tingling. Six patients withdrew from studies due to adverse events in Phase II/III. These were all reported in the post-surgical pain management studies, four in the levobupivacaine group and two in the levobupivacaine plus "other" group. The reasons for discontinuation included (Pt 0039) confusion, somnolence and agitation, (Pt.0040) severe bradycardia, (Pt 0149) pain and paresthesias. These events reported from study 030475 were all thought to be due to levobupivacaine. Pt-0002 withdrew because of what was thought to be intravascular injection of study drug. She became drowsy with slurred speech, then excited with screaming. No change in vital signs was recorded. Patient 0201 was withdrawn because of severe abnormal gait related to leg length discrepancy postoperatively, which was obviously not related to the medication. Patient 0133 was withdrawn because of severe asystole, which occurred in the setting of a pneumothorax. The patient also had a history of bradycardia preoperatively. It cannot be determined whether levobupivacaine may have contributed to this patient's conduction defect.

Overall Adverse Event Profile

Controlled trials

Incidences of adverse events were compared with controls, the data pooled for each category of study.

In the adverse event data from the pooled obstetrics studies, in which levobupivacaine (N=184) was compared to bupivacaine (N=188) there were no significant differences in the rates of adverse events (see sponsor's table 32 cited in Dr. Roberts' review of safety) for either the mother or infant.

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%).

In the postoperative pain studies levobupivacaine was compared to levobupivacaine plus "other" which included morphine, fentanyl and clonidine. There was no active control for levobupivacaine. Therefore the incidences are reflected only in the pooled phase II/III database.

The peripheral block studies compared treatment with levobupivacaine (N=210) with bupivacaine (N=146), placebo (N=32) and lidocaine with epinephrine (N=31). The treatment emergent adverse events reported in this group were generally expected with the exception of abnormal EKG. Bradycardia was not specifically reported in these studies.

From Most common AEs \geq 5%: Peripheral Block Studies (Sponsor's table 36)

AE	Levobupivacaine N=219	Bupivacaine N=146	Placebo N=32	Lidocaine N=31
EKG abn	16(7.6%)	17 (11.6%)	0 (0%)	0 (0%)

The pediatric studies were not controlled but adverse events were compared with children who received no treatment. Comparisons of the AEs between the two groups did not demonstrate any trends. One child in the levobupivacaine group experienced bradycardia responsive to atropine and a second was reported as having a ventricular arrhythmia. There were no reports of cardiac arrhythmias in the nontreated group.

Finally Adverse Events were pooled across all surgical anesthesia studies compared between those treated with levobupivacaine and bupivacaine (Sponsor's Table 43). The only adverse event with an incidence of \geq 1%, which had a two-fold higher incidence in the levobupivacaine group (3.4%), compared to the bupivacaine group (1.5%) was albuminuria. It is noted that the treatment emergent adverse event "Abnormal EKG" was not significantly different in this comparison in the levobupivacaine (3.6%) from the bupivacaine (4.3%) group.

All Phase II/III trials

The most frequently (\geq 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 adverse events reported in clinical trials with levobupivacaine do not provide support for the sponsor's assertion of an improved safety profile over bupivacaine. The adverse events seen, including those relating to the cardiovascular system are qualitatively and quantitatively similar to those seen with bupivacaine.

Special Safety Evaluation: Cardiovascular Safety

One of the principal issues in question for the sponsor, and the reason for the Division's decision to ask advice from outside advisors, is whether levobupivacaine is less cardiotoxic than the racemic mixture, bupivacaine, and whether, the Box Warning should be removed from the levo-bupivacaine label,

and other specific language added. The following summarizes the approach that was used to evaluate cardiac safety in this product.

ALSAC Transcripts

An ALSAC Meeting was held in closed session on March 24, 1997 to discuss

Preclinical Evaluation of Cardiovascular Toxicity

Numerous *in vitro* and *in vivo* studies performed to evaluate the preclinical cardiotoxicity are summarized in Dr. Goheer's pharmacology review.

The cardiac toxicity of levobupivacaine was compared to bupivacaine in an IV rat model, in pig, rabbits, in a canalized sheep model, and in pregnant and non-pregnant ewes. Further *in vivo* preclinical studies are currently being conducted or are planned to address the cardiotoxicity of Chirocaine. They are summarized below:

- Studying the direct effect of levobupivacaine and racemate on the CNS and heart in conscious sheep following close intra-arterial injection, specifically
 - CNS-direct carotid artery infusion (cardiac performance maintained)
 - Heart-direct coronary artery infusion (CNS performance maintained)
- Resuscitation after bolus cardiovascular infusion in dogs
- To simulate clinical resuscitation following bolus administration of lethal doses in conscious sheep.

No data are yet available from these studies.

From the available studies it appears that levobupivacaine may have a slightly higher safety margin than bupivacaine as demonstrated by preclinical *in vitro* and *in vivo* data as reviewed by Drs. Goheer and Jean.

Clinical Evaluation of Cardiovascular Safety

Five clinical studies and one integrated analysis of four studies were designed specifically to evaluate cardiac safety and are listed below:

- Study 030831—EKG Analysis for a Series of Chiroscience Clinical Studies
- Study 004801—Comparison of the Cardiovascular Effects of Racemic Bupivacaine and S-bupivacaine 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
- Study 012105—Statistical and Data Management Support Services for a Comparison of the Effects of Levobupivacaine and Racemic Bupivacaine on QT Dispersion and Signal Averaged ECT in Healthy Male Volunteers”

Study 030831 (EKG Analysis for a Series of Chiroscience Clinical Studies) was an integrated analysis across four completed studies: 004801, CS005, and 030721 and 030632. In this integrated study the sponsor analyzed EKG data from several studies using what were thought to be more precise methods of determining changes in QRS duration and QT intervals from all available 12-lead EKG's from these studies. The sponsor asserts that these studies were designed to test the hypothesis that levobupivacaine would have no effect on cardiac electrical parameters, notably IV conduction (QRS duration) and cardiac repolarization (QT and QT dispersion). The studies, while they examine the cardiovascular effects of levobupivacaine at clinically meaningful doses, were not adequately powered to either prove this hypothesis or for levobupivacaine to distinguish its safety profile from that of bupivacaine.

Study 004801 (Comparison of the Cardiovascular Effects of Racemic Bupivacaine and L-bupivacaine in 14 healthy male Volunteers) was a double-blind randomized crossover study in subjects dosed with bupivacaine and l-bupivacaine to CNS symptomatology (numbness of the tongue,

lightheadedness, tinnitus, dizziness, blurred vision and muscle twitch). Parameters such as stroke index, acceleration index, and ejection fraction were obtained as indicators of the effects of the drugs on myocardial contractility. Dr. DiMarco has specifically addressed the results of this portion of the study in his consultation.

In addition, EKG parameters, such as QT dispersion, PR interval, QRS duration, QT interval and QTc were compared from pre-dose to the maximum observed post-dose value. The primary endpoint was the difference in QT dispersion from pre-dose to the maximum observed post-dose value the results of which are shown in the table below.

Parameter	Levobupivacaine (maximum dose 150 mg as IV infusion)	Bupivacaine (maximum dose 110 mg as IV infusion)
QT dispersion (mean maximum)	74.0 ± 17.8	68.1 ms ± 19.1 ms
ΔQT dispersion†	12.2 ms ± 22.9 ms	17.7 ms ± 18.8 ms
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)

The estimate of treatment difference was -5.4 ms, which was not statistically significant. The secondary endpoints of PR intervals, QRS intervals, and QT intervals were also not significantly different between treatments.

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). Patients in this study were randomized to receive a maximum of 60 ml of 0.25% (150 mg) levobupivacaine or bupivacaine as an infiltration anesthesia for hernia repair. There were 67 patients in this study who had signal-averaged EKG measurements and QT dispersion measurements recorded at the following timepoints: predose, end of surgery, + 4 hours. The primary endpoint was the difference in QT dispersion from pre-dose to the maximum observed post-dose value, the results of which are shown in the table on the following page. Statistical analyses were performed on the QRS data as well.

Parameter	Levobupivacaine	Bupivacaine
Δ QT dispersion*	2.6 ms \pm 19.0 ms	3.6 ms \pm 20.9 ms
Est. treatment difference	-1 ms (NS)**	
QRS duration	135 ms \pm 35.3 ms	134.3 ms \pm 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)

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). In this study, patients received a standard dose of 20 ml of 0.75% (150 mg) levobupivacaine or bupivacaine in a randomized fashion as an epidural for abdominal surgery. A total of 29 patients had signal-averaged EKG measurements recorded for the following time points: 15 min, 30 min, 45 min, 1 h, 2 h, and 4 h. The primary endpoint was the difference in QT dispersion from pre-dose to the maximum observed post-dose value the results of which are shown in the table below. However, the QRS data were those upon which statistical analyses were performed.

Parameter	Levobupivacaine	Bupivacaine
QRS duration (mean median)	113.6 ms \pm 6.9	119.6 ms \pm 22.0
Δ QRS duration†	4.2 ms \pm 3.7 ms	4.5 ms \pm 2.6 ms
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)

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). In this study patients were randomized to receive a standard dose of 25-30 ml of 0.5% (125-150 mg) of levobupivacaine or bupivacaine as an epidural for caesarean section. Sixty-seven patients had their EKG measurements recorded and their QT dispersion calculated at the following timepoints: predose, postdose, recovery. The primary endpoint was the difference in QT dispersion from pre-dose to the maximum observed post-dose value the results of which are shown in the table on the next page. (Note: not all patients had recovery recordings).

Parameter	Levobupivacaine	Bupivacaine
QT dispersion † (mean median)	43.62 ms ± 16.13	43.53 ms ± 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)

The secondary endpoints of PR intervals, QRS intervals, and QT intervals were also not significantly different between treatments.

Overall, then there were no statistically significant differences between bupivacaine and levobupivacaine in post-dose QT dispersion and QRS duration. Dr. John P. DiMarco, Director of the Clinical Electrophysiology Lab and Associate Division Head, Cardiovascular Division, University of Virginia consulted with the FDA on the evaluation of the cardiovascular safety of levobupivacaine. As such he performed an independent review of this study and of study 004801. He concluded that based on both the hemodynamic and EKG data the cardiovascular effects of bupivacaine and levobupivacaine appear to be similar [with a trend favoring levobupivacaine]. Based on the data that he reviewed, however, he concluded that the trend was not sufficient to support a labeling claim of superiority.

Study 012105 (N=22) (Statistical and Data Management Support Services for a Comparison of the Effects of Levobupivacaine and Racemic Bupivacaine on QT Dispersion and Signal Averaged ECT in Healthy Male Volunteers). This was a randomized parallel group study following an open label treatment phase designed to compare the effects of s- and racemic bupivacaine on myocardial depolarization and repolarization as measured by QRS duration of a signal averaged EKG, and QT dispersion in healthy males. In this study as in the previous EKG study, subjects were dosed with bupivacaine and l-bupivacaine to CNS symptomatology. Doses ranged from 30-120 mg in both groups. The mean dose received in the levobupivacaine group was 56 mg and in the bupivacaine group was 48 mg. This difference was not statistically significant. The 75-mg dose was selected prospectively as a stratification point for the efficacy analysis. Stratification to 3 groups was based on dose of anesthetic given (open label phase)—stratum 1: ≤ 75 mg; stratum 2: 75mg to <150 mg; stratum 3: >150 mg. The objective of the study was to compare QT dispersion (from blinded review) and PR, QT, QTc and signal averaged QRS durations by dose of racemic- and s-bupivacaine.

Prospective positive primary endpoints included 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 durations for each treatment. The sponsor claims a statistically significant difference ($p=0.022$) on only on one secondary endpoint QTc.

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 for either stratum. There did appear to be a statistically significant difference between the two treatments with regard to the change from baseline in the QTc. This isolated finding was not, however, corroborated by other studies.

Summary

Review of the preclinical cardiovascular studies of levobupivacaine suggests that there may be a theoretical advantage of levobupivacaine over bupivacaine, however, the preclinical investigations have not been fully completed. Those that relate to the resuscitability of an animal following levobupivacaine toxicity are notably absent.

The safety profile of levobupivacaine based on exposure of 1439 patients in the NDA database appears to be of acceptable risk, and not appreciably different from that of the active controls, bupivacaine and ropivacaine used in the clinical trials where these drugs were compared. There are unquestionably cardiotoxic and neurotoxic effects which should be described in the package insert, some of these, such as bradycardia, while occurring overall at a frequency of $\leq 5\%$ led to serious complications such as prolonged hospitalization and withdrawal from treatment in some patients. The focused pharmacodynamic studies with electrocardiographic endpoints and the integrated EKG analyses across studies provided no clear evidence that levobupivacaine differs substantially from bupivacaine.

APPEARS THIS WAY
ON ORIGINAL

REQUEST FOR TRADEMARK REVIEW

Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530) NLRC

From: HFD-170 (Division of Anesthetic, Critical Care, and Addiction Drug Products)	HFD-170
Attention: Ken Nolan, Project Manager	Phone: 443-3741
Date: July 8, 1998	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: CHIROCAINE™	NDA 20-997
Established name, including dosage form: Levobupivacaine Injection, (2.5mg, 5.0mg, 7.5mg).	
Other trademarks by the same firm for companion products:	
Indications for Use (may be a summary if proposed statement is lengthy): Surgical Anesthesia & Pain Management	
Initial Comments from the submitter (concerns, observations, etc.):	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. August 95

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA # 20-997 Supplement # 000

HFD-170

Action: AP

Trade (generic) name/dosage form: Chirocaine (levobupivacaine injection) 2.5, 5.0, and 7.5 mg/mL

Applicant Deproco Therapeutic Class 2S

Indication(s) previously approved _____ Pediatric labeling of approved indication(s) is adequate _____ inadequate X _____

Indication in this application :

In adults for:

- Surgical Anesthesia epidermal (including cesarean section) intrathecal peripheral nerve block and local infiltration, oral surgery, ophthalmic surgery
- Pain Management for continuous epidural infusion, single or multiple bolus administration for post-operative, labor, or chronic pain
- Pain Management with epidural morphine, fentanyl, or clonidine

In children indicated for:

- Surgical anesthesia caudal epidural injection for surgical procedures and post-operative pain management
- Pain management post-operative pain management by ilioinguinal-iliohypogastric block

 1. PEDIATRIC LABELING IS ADEQUATE. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

X 2. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

 a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

 b. The applicant has committed to doing such studies as will be required.

X (1) Studies are ongoing,

 (2) Protocols were submitted and approved.

 (3) Protocols were submitted and are under review.

 (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

 c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

 3. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

4. EXPLAIN. If none of the above apply, explain, as necessary, on the back of this form.
EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

JS

Signature of Preparer and Title (PM, 050, MO, other)

8-5-99

Date

cc: Orig NDA#20-997 HFD-170/Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

3/96

Page 2 of 2

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA # 20-997 Supplement # 000

HFD-170

Action: AE

Trade (generic) name/dosage form: Chirocaine (levobupivacaine injection) 2.5, 5.0, and 7.5 mg/mL

Applicant Deproco Therapeutic Class 2S

Indication(s) previously approved _____ Pediatric labeling of approved
indication(s) is adequate _____ inadequate X _____

Indication in this application :

In adults for:

- Surgical Anesthesia epidermal (including cesarean section) intrathecal peripheral-nerve block and local infiltration, oral surgery, ophthalmic surgery
- Pain Management for continuous epidural infusion, single or multiple bolus administration for post-operative, labor, or chronic pain
- Pain Management with epidural morphine, fentanyl, or clonidine

In children indicated for:

- Surgical anesthesia caudal epidural injection for surgical procedures and post-operative pain management
- Pain management post-operative pain management by ilioinguinal-iliohypogastric block

1. PEDIATRIC LABELING IS ADEQUATE. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

2. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

b. The applicant has committed to doing such studies as will be required.

(1) Studies are ongoing,

(2) Protocols were submitted and approved.

(3) Protocols were submitted and are under review.

(4) If no protocol has been submitted, explain the status of discussions on the back of this form.

c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

3. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

PEDIATRIC PAGE
NDA 20-997
PAGE 2 OF 2

4. EXPLAIN. If none of the above apply, explain, as necessary, on the back of this form.
EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

ISJ
Signature of Preparer and Title (PM, 050, MO, other)

8-4-99
Date

cc: Orig NDA#20-997 HFD-170/Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

3/96

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EXCLUSIVITY SUMMARY FOR NDA # 20-997 SUPPL #000

Trade Name Chirocaine™ Generic Name levobupivacaine injection

Applicant Name Darwin Discovery

HFD # 170

PDUFA Date February 27, 1999

Approval Date if known: August 5, 1999

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES/ / NO / /

b) Is it an effectiveness supplement?

YES / / NO / /

If yes, what type? (SE1, SE2, etc.)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / X / NO / ___ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? 3 years.

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES / ___ / NO / X /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / ___ / NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-

covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

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2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / / N.A.

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / NO /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / NO /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / /

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

030632, CS-001, 030276, 030433, 006175, CS-005, 030475, CS-004, CS-006, 030742, 030428, 030721, 006154, 030543, 030737, 030700, CS-007, 030412

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a

previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

030632, CS-001, 030276, 030433, 006175, CS-005, 030475, CS-004, CS-006, 030742, 030428, 030721, 006154, 030543, 030737, 030700, CS-007, 030412

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided

substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

IND # _____ Yes / X / No / ___ / Explain: Darwin Discovery Ltd.

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Not applicable to this application.

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / ___ / NO / X /

If yes, explain: _____

/s/

Signature: _____ Date: 8-4-99

Title: Susmita Samanta
Regulatory Project Manager

/s/

Signature of for _____ Date: 8/17/99

Title: Cynthia G. McCormick, M.D.
Division Director

cc: Original NDA Division File

HFD-93 Mary Ann Holovac



Levobupivacaine Injection
NDA 20-997

ITEM 16. DEBARMENT CERTIFICATION

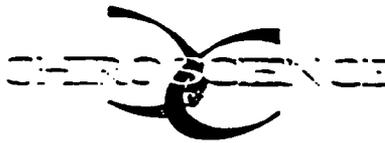
Darwin Discovery Limited certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug, and Cosmetic Act, in connection with this new drug application.

Signed on behalf of Darwin Discovery Limited by

A handwritten signature in black ink, appearing to read "B Gennery", written over a horizontal line.

Brian Gennery, Darwin Discovery Limited
Director of Development, Chiroscience R&D Limited

DATE 20 April 1998



Chirocaine™ (Levobupivacaine Injection)
NDA 20-997

ITEM 14. PATENT CERTIFICATION

Declaration under 21 CFR 314.53(c)(2)

The undersigned declares that Patent No. US 5708011 covers the method of use of levobupivacaine. This product is subject of this application for which approval is sought.

Declaration under 21 CFR 314.53(c)(3)

The applicant believes that there are no patents which claim the drug or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent is engaged in the manufacture, use or sale of the drug product.

Declaration under 21 CFR 314.108

The applicant claims exclusivity of three years from the date of approval as provided by the Drug Price Competition and Patent Term Restoration Act of 1984.

Signed on behalf of Darwin Discovery Limited by

Linda Nyari
Linda Nyari, Director of Legal Affairs

DATE 04-27-98