CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20997

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-997	**CODE:** 1S
NAME: Chirocaine™ (Levobupivacaine Injection) 0.25%, 0.5%, 0.75%.	
SPONSOR: Darwin Discovery Limited, 283 Cambridge Science Park, Milton Road, Cambridge, England	
SUBMISSION TYPE: Original NDA	**SUBMISSION DATES:** 4/ 27/98, 8/25/98,
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SYNOPSIS

The pharmacokinetics of levobupivacaine have been documented with data from twelve (12) human studies involving two hundred and thirty four (234) subjects after the different modes of administration for different surgical procedures from the perspective of the secondary effects. Human metabolism, excretion and protein binding of levobupivacaine have been adequately studied. Levobupivacaine is extensively metabolized with no unchanged levobupivacaine detected in urine or feces. Recovery of the radiolabelled dose of levobupivacaine was essentially quantitative with a mean total of about 95% being recovered in urine and feces in 48 hours. Of this 95%, about 71% was in urine while 24% was in feces. Metabolic inversion of levobupivacaine to R(+)-bupivacaine was not evident both *in vitro* and *in vivo*. *In vitro* studies using [^{14}C]Levobupivacaine showed that CYP3A4 isoform and CYP1A2 isoform mediate the metabolism of levobupivacaine to desbutyl levobupivacaine and 3-hydroxy levobupivacaine, respectively. Plasma protein binding evaluated *in vitro* showed that [^{14}C]Levobupivacaine was bound to the extent of >97% and the binding was linear in the concentration range of 0.01-1 μg/mL. The pharmacokinetics of levobupivacaine was adequately characterized. After IV infusion in healthy volunteers, the mean clearance, volume of distribution, and terminal half-life values of levobupivacaine were 39 liter/hour, 67 liters, and 1.3 hours respectively. For bupivacaine racemate, these values were very similar to those of levobupivacaine. Between the R(+)-bupivacaine and S(-)-bupivacaine enantiomers of bupivacaine, the volume of distribution was slightly higher for R(+)-bupivacaine over that of S(-)-bupivacaine. This is also evident by the higher C_{max} and AUC values for the S(-)-enantiomers of bupivacaine compared to the R(+)-enantiomer of bupivacaine. Pharmacokinetic data was also submitted after the administration of levobupivacaine and bupivacaine in patients for epidural, local infiltration, ophthalmic and peripheral nerve blocks. Overall, in all these studies, the pharmacokinetics of levobupivacaine and bupivacaine were similar. In general, the AUC values of levobupivacaine were slightly higher over those of bupivacaine. Similarly, between the R(+)-bupivacaine and S(-)-bupivacaine enantiomers of bupivacaine, the C_{max} and AUC values for the S(-)-enantiomer of bupivacaine were slightly higher compared to the R(+)-enantiomer of bupivacaine. The ratio of umbilical venous and maternal concentration of levobupivacaine, bupivacaine and the R(+)- and S(-)- enantiomers ranged from 0.252 – 0.303 after the administration of up to 150 mg of levobupivacaine and bupivacaine epidurally prior to the start of surgery for cesarean section.

RECOMMENDATION

NDA 20-997 can be approved from the viewpoint of Office of Clinical Pharmacology and Biopharmaceutics provided a mutually acceptable language can be worked out on the pharmacokinetics section of the package insert. The sponsor should submit pediatric pharmacokinetic data as soon as possible once the ongoing studies are completed.

/S/ 1/22/99

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/S/ 1/22/99

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1.0. INTRODUCTION

Bupivacaine hydrochloride, which consists of a racemic mixture of levobupivacaine (S(-)-) and dextrobupivacaine (R(+)-), has been widely marketed as a local anesthetic in the United States and throughout the world for a number of years. Bupivacaine is currently marketed in the United States with and without epinephrine in strengths of 0.25%, 0.5%, and 0.75% as Marcaine® and Sensorcaine®.

The R(+)- and S(-)- enantiomers of bupivacaine are considered to be equipotent with respect to the local anesthetic potency. However, R(+)- enantiomer is considered to have a higher central nervous system and cardiovascular toxicity relative to the S(-)- enantiomer. **Therefore, levobupivacaine, the S(-)- enantiomeric form of bupivacaine, subject of the current NDA was developed by Darwin Discovery Limited with the rationale that levobupivacaine has a lower propensity to cause CNS and CVS toxicity with an equivalent efficacy compared to bupivacaine at equivalent doses.** Data to support this rationale is submitted to Nonclinical Pharmacology and Toxicology and Clinical sections of this NDA.

Levobupivacaine is not marketed in any country at this time. A marketing license application was filed in Sweden in December of 1997 and is currently under review.

About twenty six (26) clinical trials involving fourteen hundred and six patients (1406) were conducted to demonstrate the safety and efficacy of levobupivacaine injection relative to bupivacaine for use in obstetrics, epidural anesthesia, epidural infusion for pain management, and peripheral nerve block. **Levobupivacaine is not dependent on the general circulation for exerting the regional anesthesia. However, Levobupivacaine administered for producing regional anesthesia through epidural and local infiltration is absorbed into systemic circulation where the secondary pharmacological effects such as CNS and cardiovascular toxicities occur.** The pharmacokinetics of levobupivacaine has been adequately documented with data from twelve (12) human studies involving two hundred and thirty four (234) subjects after the different modes of administration for different surgical procedures from the perspective of the secondary effects.

The proposed dosage recommendations for levobupivacaine are as follows: epidural for surgery, 50-150 mg; epidural for cesarean section, 100-150 mg; intrathecal, 15 mg; peripheral nerve block, 150 mg; ophthalmic block, 37.5-112.5 mg; local infiltration, 150 mg; dental block, 25-75 mg; bolus epidural for labor analgesia, 25-50 mg; continuous epidural for labor analgesia, 7.5-17.5 mg/hour, continuous infusion for post-operative pain, 5-25 mg/hour (the proposed package insert is attached in Appendix II). Levobupivacaine is also proposed to be used in children (down to the newborns) for local infiltration (at a dose of 1.25-2.5 mg/kg) and epidural for surgery (at a dose of 1.0-1.5 mg/kg).

2.0. PHYSICOCHEMICAL PROPERTIES & FORMULATION

Levobupivacaine HCL is a white crystalline solid that is soluble in water (>100 mg/mL). The partition coefficient (oleyl alcohol/water) is 1624 and the pKa is 8.09. The level of (R)-bupivacaine is controlled in the active ingredient specification to not more than 1.5%. Levobupivacaine Injection is a sterile, non-pyrogenic (pH 4.0-6.5) aqueous solution containing levobupivacaine hydrochloride equivalent to 2.5 mg/mL, 5.0 mg/mL, and 7.5 mg/mL of levobupivacaine base, sodium chloride for isotonicity, and Water for Injection. Sodium hydroxide and/or hydrochloric acid may be added to adjust the pH. Levobupivacaine Injection is preservative free and is available in 10 mL and 30 mL single dose vials.

3.0. LEVOBUPIVACAINE METABOLISM AND PROTEIN BINDING

Using pooled human liver microsomes (from livers of 13 individuals), kinetics of the formation of the major metabolite of both [^{14}C]Levobupivacaine and racemic [^{14}C]bupivacaine were

determined (Study 160501) and various metabolic inhibitors were added to the preparation to evaluate the specific cytochrome P450 isoforms responsible for its formation. Clinically relevant concentrations of the substrates and inhibitors were used in this *in vitro* study. [^{14}C]Levobupivacaine was found to be metabolized predominantly to 3-hydroxy- and desbutyl metabolites. Ketoconazole, an inhibitor of the CYP3A4 isoform, was found to inhibit the formation of the desbutyl levobupivacaine to the greatest degree, suggesting that the **CYP3A4 isoform of the cytochrome P450 was involved** in the formation of desbutyl levobupivacaine. Furafylline, a selective inhibitor of CYP1A2 inhibited the formation of 3-hydroxy levobupivacaine suggesting that **CYP1A2** isoform is involved in the formation of 3-hydroxy levobupivacaine.

For [^{14}C]bupivacaine, the major routes of metabolism were 3- and 4-hydroxy bupivacaine and desbutyl bupivacaine. The 3- and 4-hydroxylation pathways were shown to be mediated through CYP1A2 and dealkylation (desbutylation) through CYP3A4.

Plasma protein binding evaluated *in vitro* showed that **[^{14}C]Levobupivacaine was bound to the extent of >97%** and the binding was linear in the concentration range of 0.01-1 µg/mL (***in vitro* study 159721**). [^{14}C]Bupivacaine also exhibited similar *in vitro* plasma protein binding as that of [^{14}C]Levobupivacaine. It should be noted that whole plasma was used in this *in vitro* study and therefore it is not known as to which of the specific plasma proteins are involved in the binding of these drugs.

4.0. MASS BALANCE

This was a phase I, open label, non-randomized study conducted in four healthy male volunteers (4) investigating the plasma kinetics of levobupivacaine and total radioactivity and the rates and routes of excretion of total radioactivity following intravenous infusion (15 minutes) of 40 mg [^{14}C]-levobupivacaine (**study 011756**).

Recovery of the dose was essentially quantitative with a mean total of about 95% being recovered in urine and feces in 48 hours. Of this 95%, about 71% was in urine while 24% was in feces. HPLC analysis showed that the major component seen in the pooled urine and pooled feces samples was polar accounting for 75% and 100% of the radioactive dose excreted in urine and feces, respectively. No parent compound was seen in either of the urine and feces samples. Two other peaks were detected in the HPLC analysis of pooled urine, which accounted for about 12.2% and 12.5% of the radioactivity excreted in urine. Further investigation into the nature of the radioactivity excreted in the urine and feces indicates that the major metabolites seemed to correspond to hydroxylevobupivacaine and sulphate and glucuronide conjugates of hydroxylevobupivacaine.

The pharmacokinetic parameters of total radioactivity and levobupivacaine are shown in Table 1. **The terminal half-life of the total radioactivity is only slightly longer than that of levobupivacaine indicating the rapid elimination of the levobupivacaine dose without any accumulation of levobupivacaine and/or its metabolites.**

Table 1. Pharmacokinetic parameters of total radioactivity and levobupivacaine after a 15-minute intravenous infusion of 40 mg [^{14}C]-levobupivacaine (mean ± SD).

	C_{max} (µg equiv/mL)	$AUC_{0-\infty}$ (µg equiv. hour/mL)	$T_{1/2}$ (hour)
Total Radioactivity	2.20 ± 0.32	4.69 ± 0.32	3.3 ± 0.2
Levobupivacaine	1.80 ± 0.28	1.35 ± 0.13	2.1 ± 0.3

5.0. METABOLIC INVERSION

The level of R(+)-bupivacaine is controlled in the active ingredient specification to not more than 1.5%. Stability studies have shown no evidence of interconversion on storage. The *in vitro* chiral inversion of levobupivacaine to R(+)-bupivacaine by human liver slices was studied *in vitro* (in vitro study CHO1/932514). Even though, the concentrations of levobupivacaine declined during the incubation period, no R(+)-bupivacaine was detected in the samples analyzed (limit of detection for R(+)-bupivacaine was 2.5% of initial levobupivacaine concentrations). Similarly, no R((+)-bupivacaine was detected in the plasma samples analyzed from patients administered levobupivacaine.

6.0. INTRAVENOUS PHARMACOKINETICS

Two studies (study 030302 and study 004801) were conducted evaluating the pharmacokinetics of levobupivacaine after the administration of levobupivacaine, and those of racemic bupivacaine, R(+)- and S(-)- enantiomers after the administration of bupivacaine intravenously in healthy volunteers.

Study 030302 was a phase I, double-blind, randomized, two-way cross-over study conducted in twelve (12) healthy male volunteers. The subjects were randomized to receive one 40 mg dose of either levobupivacaine or bupivacaine as an intravenous infusion over eight (8) minutes on two occasions separated by a washout period of seven (7) days. The objective was to find out if the pharmacokinetics of levobupivacaine and bupivacaine were similar.

Plasma concentration-time profiles (mean ±s.d.) are presented in Figure 1 and mean and standard deviations of the pharmacokinetic parameters calculated are presented in Table 2. The plasma concentration-time profiles of levobupivacaine and racemic bupivacaine appear to be very similar. **The mean clearance, volume of distribution, and terminal half-life values of levobupivacaine were 39 liter/hour, 67 liters, and 1.3 hours, respectively. For bupivacaine racemate, these values were very similar to those of levobupivacaine. There was no statistical difference between any of the pharmacokinetic parameters of levobupivacaine and bupivacaine.** No formal analysis of the differences in pharmacokinetic parameters of enantiomers was performed. Even though, there do not seem to be any gross differences between R(+)- bupivacaine and S(-)-bupivacaine of the racemate, there seems to be some slight difference in the volume of distribution values between R(+)- and S(-)-enatiomers of racemic bupivacaine. S(-)-enantiomer of bupivacaine appears to have a lower volume of distribution compared to the R(+)-enantiomer of bupivacaine. This is also evident by the higher C_{max} and AUC values for the S(-)-enantiomer of bupivacaine compared to the R(+)-enantiomer of bupivacaine.

Table 2. Pharmacokinetics of levobupivacaine after the administration of 40 mg levobupivacaine, and those of racemic bupivacaine, R(+)- and S(-)- enantiomers after the administration of 40 mg bupivacaine intravenously in healthy volunteers (mean ± SD).

Parameter	Levobupivacaine	Bupivacaine Racemate	R(+)- bupivacaine	S(-)- bupivacaine
C_{max} µg/mL	1.445 ± 0.237	1.421 ± 0.224	0.629 ± 0.100	0.794 ± 0.131
AUC_{∞} µg hour/mL	1.153 ± 0.447	1.166 ± 0.400	0.478 ± 0.166	0.715 ± 0.261
$t_{\frac{1}{2}}$, hour	1.27 ± 0.37	1.15 ± 0.41	1.08 ± 0.17	1.34 ± 0.44
V_d, Liter	66.91 ± 18.23	59.97 ± 17.65	68.58 ± 21.02	56.73 ± 15.14
CL, Liter/hour	39.06 ± 13.29	38.12 ± 12.64	46.72 ± 16.07	46.72 ± 16.07

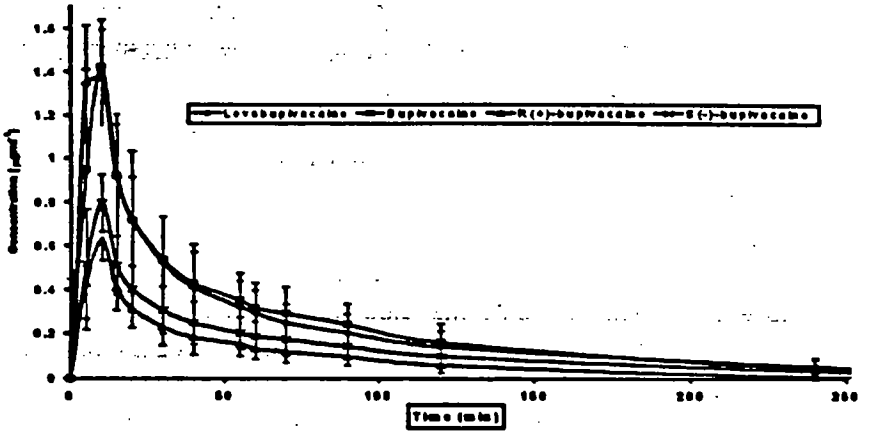

Figure 1. Concentration-Time profiles (mean ±sd) of levobupivacaine, racemic bupivacaine and R(+)- and S(-)- bupivacaine in healthy male volunteers.

Study 004801 was a Phase I double-blind, randomized, cross-over study conducted in 14 healthy male volunteers. Each volunteer was randomized to receive levobupivacaine or racemic bupivacaine (0.5%) as a constant rate infusion (2mL/minute, maximum dose of 150mg,) on two separate occasions separated by an interval of at least 7 days. The objective was to determine if doses of levobupivacaine and bupivacaine produced different degrees of cardiovascular toxicity. In addition, blood samples were taken for pharmacokinetic analysis.

Eleven patients were included in the levobupivacaine analysis, and 9 in the bupivacaine analysis. Even though the patients could be dosed up to 150 mg, the doses ranged from 22.5 mg to 110 mg for bupivacaine, while the doses ranged from 17.5 to 150 mg for levobupivacaine resulting in a varied dosing history for the different subjects.

No formal statistical analysis was performed on the pharmacokinetic parameters obtained from this study as the relatively high limit of detection of the bupivacaine isomers (0.3 µg/mL) in the assay method used in this study would result in inaccurate calculation of pharmacokinetic parameters (for most of the subjects, plasma concentrations could not be reliably quantitated past 2-4 hours). LOQ in majority of studies that used a different assay method was 10 ng/mL.

7.0. EPIDURAL PHARMACOKINETICS

No separate pharmacokinetic studies were conducted investigating the epidural pharmacokinetics of levobupivacaine. However, blood samples were obtained from a subset of patients from five clinical studies (studies 030276, 030632, CS001, 006175, and CS005) and pharmacokinetic analysis was conducted on data from these patients.

Labor

Study 030276 was a Phase III, double-blind, randomized, parallel group study comparing the efficacy, safety and pharmacokinetics of 0.25% levobupivacaine with 0.25% racemic bupivacaine in obstetric patients receiving epidural analgesia during labor. Analgesia was initiated with 10 mL (25 mg) of

study drug with the provision for patients to receive an additional seven bolus injections as top-ups (total dose of 200 mg). One hundred and sixty-nine patients in total were randomized and samples were collected from 20 patients. Blood samples were collected at 0, 10, 20, 30, 45 and 60 minutes after the first injection of study drug. The pharmacokinetic parameters calculated are presented in Table 3.

The mean C_{max} after the epidural injection of a 25 mg dose of levobupivacaine was 0.206 µg/mL. The mean C_{max} of bupivacaine was slightly lower but similar to that of levobupivacaine. Between R(+)-bupivacaine and S(-)-bupivacaine of racemic bupivacaine, the mean C_{max} of S(-)-bupivacaine was higher. Since blood samples were collected for up to 1 hour only after administration of study drug, a reliable estimate of the terminal rate constant cannot be obtained and use of $AUC_{0\text{-}60minutes}$ even for gross comparisons is not appropriate.

Table 3. Pharmacokinetic parameters of levobupivacaine, racemic bupivacaine, R(+)- bupivacaine and S(-)- bupivacaine in patients in labor.

Parameter	0.25% Levobupivacaine	0.25% Bupivacaine	R(+)- bupivacaine	S(-)- bupivacaine
C_{max} µg/mL	0.206 ±0.038	0.183 ±0.076	0.087 ±0.031	0.103 ±0.037
t_{max} hour	0.27 ±0.05	0.27 ±0.09	0.30 ±0.14	0.28 ±0.07
$AUC_{0\text{-}60\ minutes}$ µg hour/mL	0.132 ±0.031	0.089 ±0.061	0.036 ±0.029	0.051 ±0.034

Caesarian section

Study 030632 was a Phase III double-blind, randomized, controlled trial comparing the efficacy and safety of 0.5% levobupivacaine with 0.5% bupivacaine in patients undergoing elective Caesarian section performed under epidural anesthesia. Epidural blocks were initiated with 25 mL of study drug (125mg) with the option of an additional 5 mL (total dose 150mg) prior to the start of surgery (100-150 mg is recommended in the proposed package insert). Sixty-seven patients in total were randomized to the study, blood samples from 19 patients were evaluated for pharmacokinetic analysis. The results of the pharmacokinetic analysis are presented in Table 4, and the mean concentration-time profiles are presented in Figure 2.

Table 4. Pharmacokinetic parameters (mean ±sd) of 0.5% levobupivacaine, 0.5% bupivacaine racemate, R(+)- bupivacaine and S(-)- bupivacaine in patients undergoing elective Caesarian section

Parameter	0.5% Levobupivacaine	0.5% Bupivacaine	R(+)- bupivacaine	S(-)- bupivacaine
C_{max} µg/mL	1.137 ±0.321	1.135 ±0.402	0.535 ±0.175	0.601 ±0.229
t_{max} hour	0.56 ±0.12	0.55 ±0.19	0.55 ±0.19	0.52 ±0.18
$AUC_{0\text{-}\infty}$ µg hour/mL	3.289 ±0.774	3.041 ±0.663	1.470 ±0.349	1.571 ±0.325

The mean C_{max} after the epidural injection of a 150 mg dose of levobupivacaine was 1.137 µg/mL. The mean C_{max} of bupivacaine was similar to that of levobupivacaine.

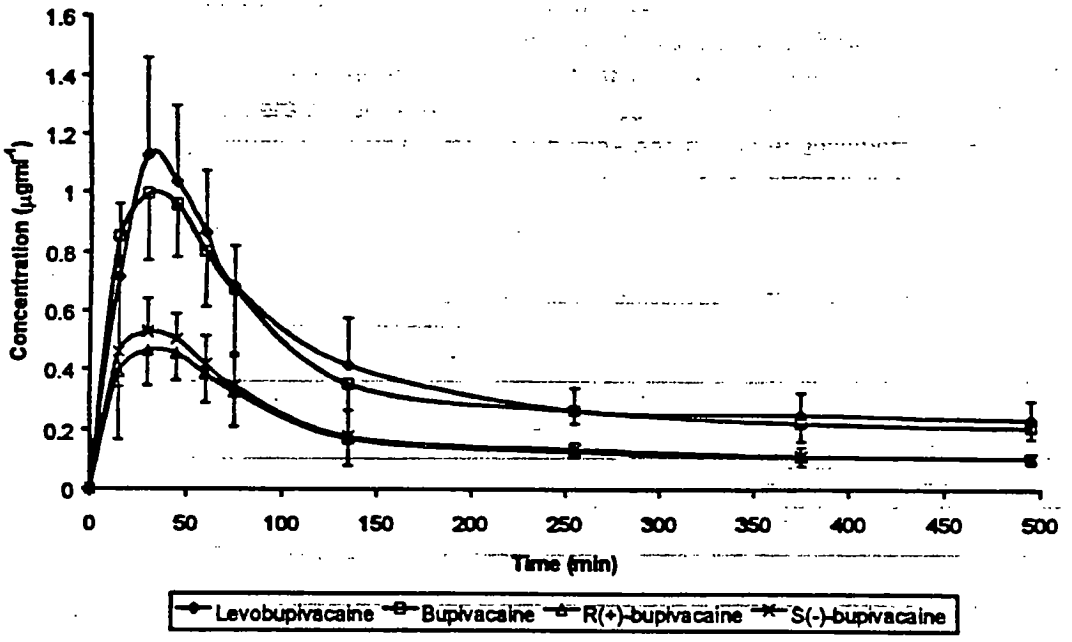

Figure 2. Concentration time profiles (mean ±sd) of levobupivacaine, racemic bupivacaine and R(+)- and S(-)- bupivacaine in patients undergoing elective Caesarian section.

Study CS001 was a Phase III double-blind, randomized, controlled trial comparing the efficacy and safety of 0.5% levobupivacaine with 0.5% bupivacaine in patients undergoing elective Caesarian section performed under epidural anesthesia. Up to 30 mL (total dose of 150 mg) study drug was administered prior to surgery (100-150 mg is recommended in the proposed package insert).. Sixty-three patients in total were randomized with samples collected from 18 evaluable patients. The results of the pharmacokinetic analysis are presented in Table 5.

Table 5. Pharmacokinetic parameters of levobupivacaine, bupivacaine and the R(+)- and S(-)- enantiomers in patients undergoing elective Caesarian section.

Parameter	0.5% Levobupivacaine	0.5% Bupivacaine	R(+)- bupivacaine	S(-)- bupivacaine
C_{max} µg/mL	1.207 ± 0.388	1.102 ± 0.356	0.505 ± 0.166	0.600 ± 0.190
T_{max} hour	0.49 ± 0.23	0.53 ± 0.27	0.55 ± 0.27	0.45 ± 0.23
AUC_{0-24} µg hour/mL	4.722 ± 1.198	3.846 ± 0.833	1.816 ± 0.398	2.030 ± 0.444

The mean C_{max} after the epidural injection of a 150 mg dose of levobupivacaine was 1.207 µg/mL. The mean C_{max} of bupivacaine was similar but slightly lower than that of levobupivacaine. Between R(+)-bupivacaine and S(-)-bupivacaine of racemic bupivacaine, the mean C_{max} and AUC_{0-24} of S(-)-bupivacaine were higher over those of R(+)-bupivacaine. The results obtained in this

study correspond to the same general differences seen between levobupivacaine, bupivacaine, R(+)-bupivacaine and S(-)-bupivacaine seen in study 030632.

In Patients Undergoing Elective Lower Limb Surgery

Study 006175 was a Phase III double-blind, randomized, parallel group trial comparing the efficacy, plasma concentrations and safety profiles of two different concentrations of levobupivacaine (0.5% and 0.75%) with 0.5% racemic bupivacaine in patients undergoing elective lower limb vascular surgery or arthroscopy performed under epidural anesthesia. Patients were administered 15 mL (75 to 112.5 mg) of study drug (50-150 mg is recommended in the proposed package insert). Eighty-eight patients were recruited into the study from which blood samples from 26 patients were evaluable for the pharmacokinetic analysis. Blood samples were taken pre-dose, and at 10, 20, 30, 45 minutes and at 1, 1.5, 2, 4, 6, 8, 10 and 24 hours after injection of the study drug. Table 6 shows the pharmacokinetic parameters calculated.

Table 6. Pharmacokinetic parameters of 0.5% and 0.75% levobupivacaine, 0.5% bupivacaine and the R(+)- and S(-)-enantiomers in patients undergoing elective surgery under epidural anesthesia.

Parameter	0.5% Levobupivacaine	0.75% Levobupivacaine	0.5% Bupivacaine	R(+)-Bupivacaine	S(-)-Bupivacaine
C_{max} µg/mL	0.582 ± 0.25	0.811 ± 0.341	0.414 ± 0.162	0.188 ± 0.075	0.227 ± 0.088
t_{max} hour	0.52 ± 0.14	0.44 ± 0.19	0.36 ± 0.08	0.36 ± 0.08	0.44 ± 0.29
AUC_{0-24} µg hour/mL	3.561 ± 1.483	4.93 ± 1.846	2.044 ± 1.190	0.707 ± 0.437	1.212 ± 0.730

Between 0.5% and 0.75% levobupivacaine (75 mg and 112.5 mg), the mean C_{max} and AUC_{0-24} of levobupivacaine were approximately dose-proportional (the values were about 1.4 fold higher for 0.75% levobupivacaine over those of 0.5% levobupivacaine). The mean C_{max} after the epidural injection of a 75 mg dose of 0.5% levobupivacaine was 0.582 µg/mL. The mean C_{max} of 0.5% bupivacaine was similar but slightly lower than that of levobupivacaine. Between R(+)-bupivacaine and S(-)-bupivacaine of racemic bupivacaine, the mean C_{max} and AUC_{0-24} of S(-)-bupivacaine were higher over those of R(+)-bupivacaine.

In Patients Undergoing Major Elective Abdominal Surgery

Study CS 005 was a Phase III double-blind, randomized controlled trial comparing the efficacy and safety of 0.75% levobupivacaine with 0.75% bupivacaine in patients undergoing major abdominal surgery. Each patient received 20 mL of study drug (150 mg) prior to surgery, with allowance for top-ups (50-150 mg is recommended in the proposed package insert). Twenty-two patients had multiple blood samples withdrawn (at 0, 15, 30, 45 minutes and 1, 2, 4, 6, 8 and 10 hours post dose). **Variability in the number and timing of the top-up dosages given meant that the pharmacokinetic parameters for this group could not be calculated with confidence.**

8.0. BRACHIAL PLEXUS PHARMACOKINETICS

Study 006154 was a Phase III double-blind, randomized, parallel group trial comparing the efficacy, plasma concentrations, and safety profiles of two different concentrations of levobupivacaine (0.5% and 0.25%) with 0.5% racemic bupivacaine in patients undergoing elective hand surgery performed under local anesthesia with a supraclavicular brachial plexus block. Each patient received a dose of 0.4 mL/kg (2 mg/kg or 3 mg/kg levobupivacaine and 2 mg/kg bupivacaine). The recommended dose in the proposed package insert is 150 mg of 0.5% levobupivacaine. Seventy-six patients in total were recruited into this study of which blood samples were collected from 30 evaluable patients. Blood samples were collected pre-dose, and at 10, 20, 30, 45 minutes and 1, 1.5, 2, 4, 6, 8, 10 and 24 hours after injection of study drug. Plasma concentration time curves (mean ±sd) are presented in Figure 3 and a summary of the pharmacokinetic variables in Table 7.

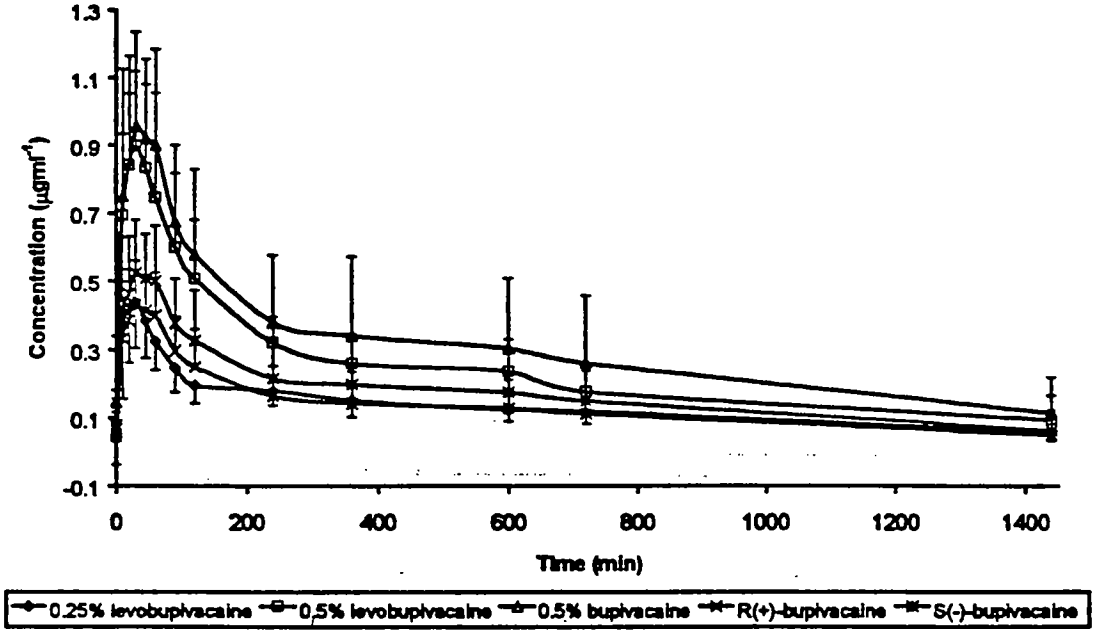

Figure 3. Concentration time profiles of 0.25% and 0.5% levobupivacaine, 0.5% bupivacaine and R(+)- and S(-)- enantiomers in patients undergoing brachial plexus block.

Between 0.25% and 0.5% levobupivacaine, the mean C_{max} and AUC_{0-24} of levobupivacaine were approximately dose-proportional (the values were about 2 fold and 1.8 fold higher, respectively, for 0.5% levobupivacaine over those of 0.25% levobupivacaine). **The mean C_{max} and AUC_{0-24} of 0.5% bupivacaine were similar but slightly higher than those of 0.5% levobupivacaine.** Between R(+)-bupivacaine and S(-)-bupivacaine of racemic bupivacaine, the mean C_{max} and AUC_{0-24} of S(-)-bupivacaine were higher over those of R(+)-bupivacaine.

Table 7. Pharmacokinetic parameters of 0.25 and 0.5% levobupivacaine, 0.5% bupivacaine and the R(+)- and S(-)-enantiomers in patients undergoing brachial plexus block.

	0.25% Levobupivacaine	0.5% Levobupivacaine	0.5% Bupivacaine	R(+)-Bupivacaine	S(-)-Bupivacaine
C_{max} (µg/mL)	0.474 ± 0.189	0.961 ± 0.282	1.029 ± 0.307	0.465 ± 0.139	0.568 ± 0.139
t_{max} (hour)	0.5 ± 0.16	0.7 ± 0.34	0.7 ± 0.23	0.7 ± 0.26	0.68 ± 0.23
AUC_{0-36} (hour µg/mL)	2.999 ± 0.767	5.311 ± 1.662	6.832 ± 3.925	2.952 ± 1.677	3.881 ± 2.264
$T_{\frac{1}{2}}$ (hour)	19.7 ± 22.7	19.5 ± 22.8	12.8 ± 7.9	13.6 ± 7.6	12.6 ± 7.4

9.0. INFILTRATION PHARMACOKINETICS

Pharmacokinetic data was submitted on infiltration route of pharmacokinetics from two clinical studies (studies 030428 and 030721). Both studies were Phase III double-blind, randomized, parallel group trials comparing the efficacy, safety and pharmacokinetics of 0.25% levobupivacaine with 0.25% bupivacaine when used for ilioinguinal/infiltration anesthesia in patients undergoing elective inguinal hernia repair. Anesthesia was initiated with 50 mL of study drug (125mg), an additional 10ml could be administered during the course of surgery (total dose of up to that recommended in the package insert-150mg).

In Study 030721 the additional amount given varied between 1 and 10 mL and was given at varying times after the initial administration of the drug, sometimes even in different stages. Therefore, variability in the dosage regimen meant that calculation of pharmacokinetic parameters could not be conducted on the 21 patients who had pharmacokinetic samples taken in this study.

In Study 030428 Twenty patients were recruited for pharmacokinetics evaluation, of which 17 were evaluable (9 levobupivacaine, 8 bupivacaine). Blood samples were taken before the final dose increment and at 5, 15, 30, 45 minutes, 1, 1.5, 2, 3 and 4 hours post-dose. The summary of the pharmacokinetic parameters is presented in Table 8. Since blood samples were collected for up to 4 hours only after administration of study drug, a reliable estimate of the terminal rate constant cannot be obtained. Also, each of the subsequent doses were given at different times to the patient implying that the peak and time to peak concentrations and AUC_{0-t} values can only be used for making gross comparisons. The C_{max} and AUC_{0-t} were higher for S(-)-bupivacaine over R(+)-bupivacaine after the administration of 0.25% racemic bupivacaine following the general trend seen in other studies. **Between levobupivacaine and racemic bupivacaine, the C_{max} was lower and the AUC was similar for levobupivacaine compared to bupivacaine.**

Table 8. A summary of the pharmacokinetic parameters of racemic bupivacaine, the R(+)- and S(-)- enantiomers, and levobupivacaine after ilioinguinal/infiltration anesthesia.

Parameter	0.25% Levobupivacaine	0.25% Bupivacaine	R(+)-Bupivacaine	S(-)-Bupivacaine
C_{max} µg/mL	0.381 ± 0.156	0.418 ± 0.155	0.184 ± 0.065	0.234 ± 0.090
t_{max} hour	0.56 ± 0.52	0.32 ± 0.25	0.29 ± 0.14	0.32 ± 0.25
AUC_{0-t} µg hour/mL	1.128 ± 0.559	1.090 ± 0.395	0.464 ± 0.160	0.626 ± 0.235

10.0. PERIBULBAR BLOCK PHARMACOKINETICS

This was a Phase III double-blind, randomized, parallel group trial comparing the efficacy and safety of 0.75% levobupivacaine with 0.75% bupivacaine in sixty (60) patients undergoing elective ophthalmic anterior segment surgery performed under peribulbar block (study 030737). Ophthalmic block was achieved with a total dose of 37.5 mg (sponsor's proposed dosage recommendation is 37.5 – 112.5 mg). Pharmacokinetics were determined from twenty (20) of the sixty (60) patients. Blood samples were collected pre-dose and at 10, 15, 30, 45 minutes and 1, 2 and 4 hours after administration of study drug. A summary of the pharmacokinetic parameters is presented in Table 9. Since blood samples were collected for up to 4 hours only after administration of study drug, a reliable estimate of the terminal rate constant cannot be obtained. Therefore, emphasis is on the peak and time to peak concentrations only and AUC_{0-t} values should be viewed with caution (AUC_{0-t} is to be used for gross comparisons). The mean C_{max} was 0.41 µg/mL after the administration of a 37.5 mg dose of 0.75% levobupivacaine. **Between levobupivacaine and racemic bupivacaine, C_{max} and AUC_{0-t} of levobupivacaine were 147% and 125% of that racemic bupivacaine.** As was found in other studies, the C_{max} and AUC_{0-t} were higher for S(-)-bupivacaine over R(+)-bupivacaine after the administration of 0.75% racemic bupivacaine.

Table 9. A summary of the pharmacokinetic parameters of racemic bupivacaine, the R(+)- and S(-)-enantiomers, and levobupivacaine after peribulbar block.

Parameter	0.75% Levobupivacaine	0.75% Bupivacaine	R(+)-Bupivacaine	S(-)-Bupivacaine
C_{max} µg/mL	0.410 ± 0.145	0.281 ± 0.096	0.122 ± 0.043	0.159 ± 0.053
t_{max} hour	0.32 ± 0.17	0.36 ± 0.25	0.36 ± 0.25	0.43 ± 0.32
AUC_{0-t} µg hour/mL	0.548 ± 0.128	0.439 ± 0.120	0.185 ± 0.050	0.254 ± 0.071

11.0. SPECIAL POPULATIONS

No separate studies were conducted investigating the pharmacokinetics of levobupivacaine in renal failure, hepatic failure, and pediatric populations. Available information on bupivacaine was summarized from the literature in renal failure and hepatic failure patients. *In vitro* drug-drug interactions were examined between levobupivacaine and other drugs such as morphine, clonidine, sufentanil, and fentanil. An attempt was made to isolate gender and age (i.e. elderly) effects from the pharmacokinetic studies.

11.1. Hepatic Failure

Mather, McCall and McNicol (*Bupivacaine enantiomer pharmacokinetics after intercostal neural blockade in liver transplantation patients. Anesth. Analg. 1995; 80: 328-335*), have studied 12 patients who have received bupivacaine as an intercostal block following orthoptic liver transplant. In these patients the transplanted liver takes a period of a few days to recover its normal function after surgery and this is the closest situation found in the literature to patients with liver dysfunction receiving bupivacaine. Pharmacokinetic analysis shows that the elimination of the drug in such patients is prolonged, as can be expected in a drug extensively metabolized in the liver. However, the design of the study (no control group, extravascular route of administration, different dosage regimen etc.) is such that no meaningful

information is available from this study to quantify the degree of alteration in the pharmacokinetics of bupivacaine in this patient population other than coming to a conclusion of impaired clearance based on comparison with historical data.

11.2. Renal Failure

Rice, Pither and Tucker (*Reference: Plasma concentrations of bupivacaine after supraclavicular brachial plexus blockade in patients with chronic renal failure. Anesthesia, 1991; Vol 46: 354-357.*) describe a study in which they compared 10 normal patients with 10 patients having chronic renal failure (classification based on serum creatinine, serum urea, and serum alpha-1-acid glycoprotein which were significantly elevated), undergoing a brachial plexus block with 0.5% bupivacaine. Neither the block characteristics nor the pharmacokinetic parameters were influenced by the presence of renal dysfunction (mean C_{max} and AUC values were 99% and 116% of that of the control group). This finding is expected for a drug where urinary excretion is not extensive.

11.3. Elderly

The sponsor attempted retrospectively to tease out age effect from already conducted pharmacokinetic studies. Four studies had a spread of age groups, study 030737 (peribulbar block), 030428 (ilioinguinal/infiltration anesthesia), 006154 (brachial plexus block) and 006175 (epidural anesthesia). As the 4 studies involve the administration of the study drug at a variety of different sites, and at a variety of different concentrations, no attempt has been made to pool the data. In particular, the blood supply at the sites chosen for each study would differ markedly and significantly alter the absorption characteristics from that site. Therefore, the sponsor chose to discuss each study on the data from each study discretely.

The limited data indicate that whilst there are some differences in t_{max}, C_{max} and AUC for levobupivacaine and bupivacaine with regards to age (between age groups of >65, 65-75, and >75 years), these are small and vary depending on the site of administration but the observations are based on small numbers. Thus there appears to be no data to suggest a clinically significant difference in the pharmacokinetic characteristics caused by age changes.

11.4. Gender

The sponsor attempted retrospectively to tease out gender effect from already conducted pharmacokinetic studies. However, the small number of subjects in either of the male and female groups, the different routes of administration (data could not be pooled) in the different studies did not permit the assessment of a consistent trend.

12.5. Pediatrics

No data on the pharmacokinetics of levobupivacaine in pediatrics has been submitted. However, efficacy data via infiltration and epidural blocks in children aged from six months to 12 years was submitted to the clinical section of the NDA.

12.6. Maternal/Fetal Ratio

Post delivery maternal and umbilical vein concentrations of levobupivacaine, bupivacaine, and the R(+)- and S(-)- enantiomers of bupivacaine were examined in studies 030276, 030632 and CS 001. All three studies involved epidural anesthesia, 030276 in patients in labor, and 030632 and CS 001 in

patients undergoing elective Caesarian section. The results of the post delivery maternal and umbilical vein concentration, along with the ratio between the two, are presented in Table 10.

The Caesarian section studies, 030632 and CS001 both concluded with similar results, with **the ratio of umbilical venous and maternal concentration of levobupivacaine, bupivacaine and the R(+)- and S(-)- enantiomers ranging from 0.252 – 0.303.** Study 030276, in patients receiving analgesia during labor, exhibited much lower ratio's for bupivacaine and its two enantiomers (0.081 – 0.092). It is not clear if this is an artifact or real (the %CV for the umbilical vein concentration is about 208% while it is 46% for maternal concentration for 0.25% bupivacaine).

Table 10. Post delivery maternal and umbilical vein plasma concentrations of levobupivacaine, bupivacaine and the R(+) and S(-) enantiomers of bupivacaine.

		Maternal concentration	Umbilical vein concentration	Ratio (Uv/Ma)
Study 030276	0.25% levobupivacaine	0.393 ± 0.142	0.112 ± 0.067	0.285
	0.25% bupivacaine	0.287 ± 0.131	0.025 ± 0.052	0.087
	R(+)- enantiomer	0.135 ± 0.070	0.011 ± 0.025	0.081
	S(-)- enantiomer	0.152 ± 0.062	0.014 ± 0.028	0.092
Study 030632	0.25% levobupivacaine	0.847 ± 0.274	0.221 ± 0.115	0.252 ± 0.094
	0.25% bupivacaine	0.827 ± 0.267	0.217 ± 0.105	0.272 ± 0.109
	R(+)- enantiomer	0.394 ± 0.128	0.103 ± 0.050	0.275 ± 0.108
	S(-)- enantiomer	0.433 ± 0.141	0.114 ± 0.055	0.270 ± 0.110
Study CS 001	0.25% levobupivacaine	0.900 ± 0.273	0.266 ± 0.106	0.303 ± 0.145
	0.25% bupivacaine	0.767 ± 0.215	0.191 ± 0.112	0.254 ± 0.110
	R(+)- enantiomer	0.347 ± 0.090	0.087 ± 0.052	0.268 ± 0.105
	S(-)- enantiomer	0.421 ± 0.118	0.104 ± 0.062	0.256 ± 0.112

12.7. Drug-Drug Interactions

Using pooled microsomal preparations, potential interactions involving levobupivacaine and other co-administered analgesics such as morphine, fentanyl, clonidine and sufentanil was investigated *in vitro* (**Study 163282**). Incubations were performed in the absence and presence of clinically relevant concentrations of morphine, fentanyl, clonidine and sufentanil to find out the effect on the [^{14}C]-Levobupivacaine and [^{14}C]-Bupivacaine metabolism. Morphine, fentanyl, and clonidine did not show any inhibition of [^{14}C]-levobupivacaine or [^{14}C]-bupivacaine metabolism. At concentrations 100-1000 fold greater than reported plasma concentrations, sufentanil showed a small degree of inhibition of the [^{14}C]-Levobupivacaine and [^{14}C]-Bupivacaine metabolism. Therefore, **none of the drugs tested in this study, morphine, fentanyl, clonidine, and sufentanil are likely to have an inhibitory effect on the oxidative metabolism of levobupivacaine and bupivacaine.**

However, none of these tested compounds was an inhibitor of the CYP3A4 or CYP1A2 isoforms and it is conceivable that the metabolism of levobupivacaine may likely be affected by the known CYP3A4 inducers (such as phenytoin, phenobarbital, rifampin), CYP3A4 inhibitors (azole antimycotics, certain protease inhibitors, macrolide antibiotics, and calcium channel antagonists), CYP1A2 inducers (omeprazole) and CYP1A2 inhibitors (furafylline and clarithromycin).

12.0. ANALYTICAL METHODOLOGY

13.0. CONCLUSIONS

1. Levobupivacaine is extensively metabolized with no unchanged levobupivacaine detected in urine or feces. Recovery of the radiolabelled dose of levobupivacaine was essentially quantitative with a mean total of about 95% being recovered in urine and feces in 48 hours. Of this 95%, about 71% was in urine while 24% was in feces. The mean elimination half-life of total radioactivity in plasma was 3.3 hours.
2. *In vitro* studies using [^{14}C]Levobupivacaine showed that CYP3A4 isoform and CYP1A2 isoform mediate the metabolism of levobupivacaine to desbutyl levobupivacaine and 3-hydroxy levobupivacaine, respectively.
3. Metabolic inversion of levobupivacaine to R(+)-bupivacaine was not evident both *in vitro* and *in vivo*.
4. Plasma protein binding evaluated *in vitro* showed that [^{14}C]Levobupivacaine was bound to the extent of >97% and the binding was linear in the concentration range of μg/mL.
5. After IV infusion, the mean clearance, volume of distribution, and terminal half-life values of levobupivacaine were 39 liter/hour, 67 liters, and 1.3 hours respectively.
6. For bupivacaine racemate, the pharmacokinetic parameter values were very similar to those of levobupivacaine after intravenous infusion. Even though, there does not seem to be any gross differences between the pharmacokinetic parameters of R(+)- bupivacaine and S(-)-bupivacaine of the racemate, the volume of distribution of S(-)-enantiomer of racemic bupivacaine seems to be slighly lower.
7. Pharmacokinetic data was submitted at the recommended doses for epidural block for surgery, local infiltration and peripheral nerve blocks (brachial plexus).
8. Pharmacokinetic data was submitted at doses bracketed in the recommended dosage regimen for epidural for labor, epidural for cesarean section, and ophthalmic block.

9 Pharmacokinetic differences were observed between R(+)- bupivacaine and S(-)-bupivacaine of bupivacaine in a majority of studies that evaluated levobupivacaine for the proposed indications, with higher mean values of C_{max} and AUC for S(-)-bupivacaine over those of R(+)- bupivacaine. Between levobupivacaine and racemic bupivacaine, the AUC values were very similar but slightly higher for levobupivacaine at equivalent doses.

10 The ratio of umbilical venous and maternal concentration of levobupivacaine, bupivacaine and the R(+)- and S(-)- enantiomers ranged from 0.252 – 0.303 after the administration of up to 150 mg of levobupivacaine and bupivacaine epidurally prior to the start of surgery for cesarean section.

11 Pharmacokinetic data was not submitted supporting the use of levobupivacaine in children, in dental pain, continuous infusion for pain relief in labor, and intrathecal block.

14.0. PROPOSED PACKAGE INSERT

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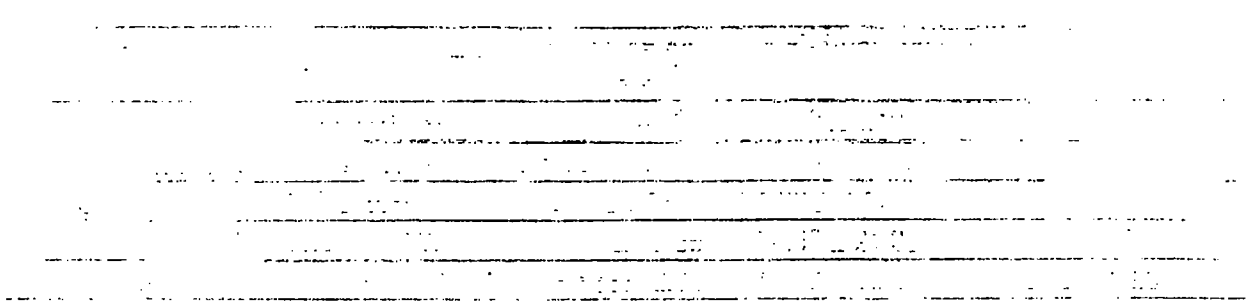
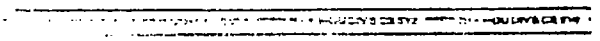
pages of trade secret and/or confidential commercial information

APPENDIX I





MASS BALANCE

Study Type: Mass balance.
Study Title: The Excretion and Plasma Kinetics Of [^{14}C]-Levobupivacaine In Man Following the Single Intravenous Administration.
NDA: 20-997 Submission Date: April 27, 1998 Volume: 1.23 Protocol: 011756
Clinical Investigator: Analytical Investigator:

Single Dose: Yes Cross-over: No Other Design: Open, non-randomized
Fasted: yes (10 hour overnight)

Subject Breakdown
Normal Yes Young Yes
N= 4 M= 4
Weight Mean 78 kg Range 68-90 kg
Age Mean 47 yrs Range 41-55 yrs
Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
[^{14}C]Levobupivacaine	40 mg	Solution	2.67 mg/mL	CFQ9713

Analytical Methodology

Labeling Claims
Elimination is principally via the urine. Following intravenous administration of carbon-14 levobupivacaine to man (N=4) recovery of the dose was quantitative for all subjects (>96%). The major proportion of the administered radioactivity was excreted in the urine (mean 71.7% of recovered dose), radioactivity excreted in the feces accounted for a mean of 25.1% of the recovered dose. In the first 48 hours after administration 94.6% of the dose was recovered.

Results and Discussion
Study 011756 examined the pharmacokinetics of levobupivacaine in 4 healthy male volunteers who received 40mg of [^{14}C]Levobupivacaine intravenously over 15 minutes. Figure 1 shows the individual concentration versus time profiles of levobupivacaine (Data presented to 150 minutes to observe the initial profile). Levobupivacaine was undetectable in the blood in all subjects by 12 hours.

The pharmacokinetic parameters of total radioactivity and levobupivacaine are shown in Table 1. The terminal half-life of the total radioactivity is only slightly longer than that of levobupivacaine indicating the relatively rapid elimination of the levobupivacaine dose.

Recovery of the total radioactivity dose was essentially quantitative with a mean total of about 95% being recovered in urine and feces in 48 hours. Of this 95%, about 71% was in urine while 24% was in feces. [redacted] analysis showed that the major component seen in the pooled urine and pooled feces samples was polar accounting for 75% and 100% of the radioactive dose excreted in urine and feces, respectively. Two other peaks were detected in the [redacted] analysis of pooled urine, which accounted for about 12.2% and 12.5% of the radioactivity excreted in urine. No parent compound was seen in either of the urine and feces samples. Further investigation into the nature of the radioactivity excreted in the urine and feces indicates that the major metabolites seemed to correspond to hydroxylevobupivacaine and sulphate and glucuronide conjugates of hydroxylevobupivacaine.

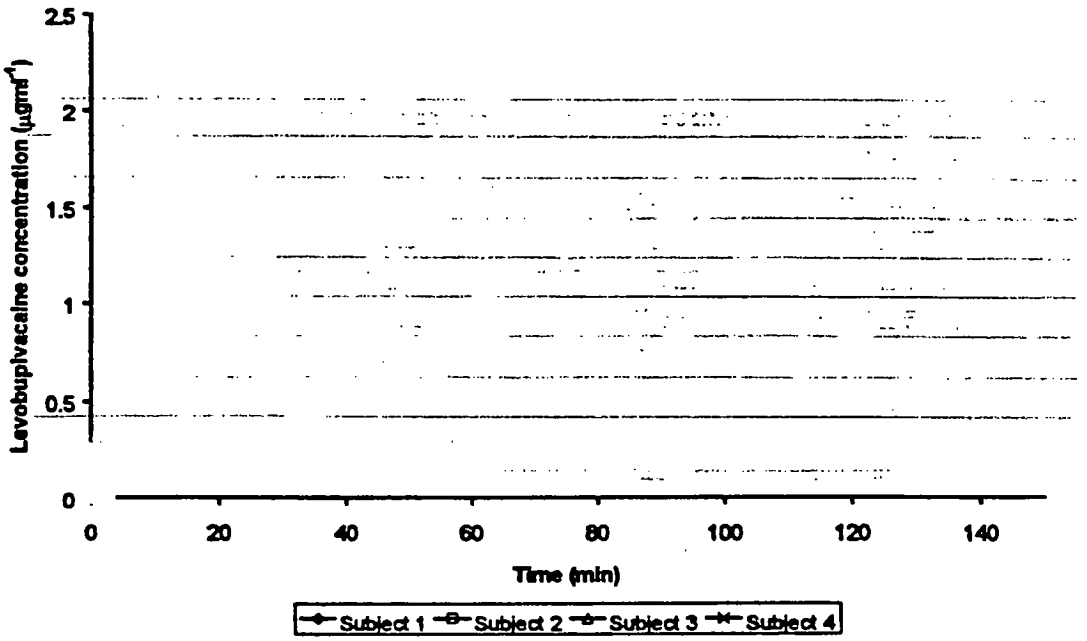


Figure 1. Concentration time profiles of 4 patients administered 40mg of [^{14}C]Levobupivacaine intravenously.

Table 1. Pharmacokinetic parameters of total radioactivity and levobupivacaine after a 15 minute intravenous infusion of 40 mg [^{14}C]-levobupivacaine (mean ± SD).

	C_{max} (µg equiv/mL)	T_{max} (hour)	AUC_{0-t} (µg equiv.hour/mL)	$AUC_{0-\infty}$ (µg equiv. hour/mL)	$T_{1/2}$ (hour)
Total Radioactivity	2.20 ± 0.32	0.25 ± 0.00	4.13 ± 0.25	4.69 ± 0.32	3.3 ± 0.2
Levobupivacaine	1.80 ± 0.28	0.25 ± 0.00	1.31 ± 0.13	1.35 ± 0.13	2.1 ± 0.3

INTRAVENOUS PHARMACOKINETICS

Study Type: Pharmacokinetics
Study Title: Pharmacokinetics of Levobupivacaine and Bupivacaine after Intravenous Administration.
NDA: 20-997 Submission Date: April 27, 1998 Volume: 1.24 Protocol:030302
Clinical Investigator: Analytical Investigator:

Single Dose: Yes Cross-over: Yes Other Design: Randomized
Fasted: yes (overnight) Washout-period: 6 days

Subject Breakdown
Normal Yes Young Yes
N= 12 M=12
Weight Mean 77 kg Range 63-96 kg
Age Mean 29 yrs Range 20-52 yrs

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
Bupivacaine	40 mg	Sterile solution	0.5%	VC178
Levobupivacaine	40 mg	Sterile Solution	0.5%	2372K

Analytical Methodology

Labeling claims
Comparative pharmacokinetic parameters following intravenous administration are presented in the following table:

Mean Pharmacokinetic Data:

Study:		030302	
		Levobupivacaine	Bupivacaine
Enantiomer measured:		S(-)	S(-) + R(+)
Dose received (mg):		40	40
n		11	11
Cmax	(µg/ml)	1.44	1.42
$AUC_{(0-inf)}$	(µg.min/ml)	69.2	70.0
Tmax	(min)	10.2	10.2
t½	(min)	76.8	69.2
Cl	(l/min)	0.65	0.64
Vd	(l)	66.9	60.0
MRT	(min)	85.4	84.5

Results and Discussion

Study 030302 was a Phase I double-blind randomized cross-over study conducted in twelve (12) healthy male volunteers. Each subject was randomized to receive one 40mg dose of levobupivacaine or one 40mg dose of bupivacaine on two occasions separated by an interval of seven days. Doses were administered intravenously in a volume of 8mL over 8 minutes. Eleven patients were evaluable for analysis.

Plasma concentration-time profiles (mean ±sd) are presented in Figure 1 and mean and standard deviations of the pharmacokinetic parameters calculated are presented in Table 1. The plasma concentration-time profiles of levobupivacaine and racemic bupivacaine appear to be very similar. The mean clearance, volume of distribution, and terminal half-life values of levobupivacaine were 39 liter/hour, 67 liters, and 1.3 hours respectively. For bupivacaine racemate, these values were very similar to those of levobupivacaine. There was no statistical difference between any of the pharmacokinetic parameters of levobupivacaine and bupivacaine. No formal analysis of the differences in pharmacokinetic parameters of enantiomers was performed. Even though, there do not seem to be gross differences between R(+)-bupivacaine and S(-)-bupivacaine of the racemate, there seems to be some slight difference in the volume of distribution values between R(+)- and S(-)-enatiomers of racemic bupivacaine. S(-)-enantiomer of bupivacaine appears to have a lower volume of distribution compared to the R(+)-enantiomer of bupivacaine. This is also evident by the higher C_{max} and AUC values for the S(-)-enantiomer of bupivacaine compared to the R(+)-enantiomer of bupivacaine.

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Table 1. Pharmacokinetics of levobupivacaine after the administration of 40 mg levobupivacaine, and those of racemic bupivacaine, R(+)- and S(-)- enantiomers after the administration of 40 mg bupivacaine intravenously in healthy volunteers (mean ± SD).

Parameter	Levobupivacaine	Bupivacaine racemate	R(+)- bupivacaine	S(-)- bupivacaine
C_{max} µg/mL	1.445 ± 0.237	1.421 ± 0.224	0.629 ± 0.100	0.794 ± 0.131
$AUC_{0-\infty}$ µg hour/mL	1.153 ± 0.447	1.166 ± 0.400	0.478 ± 0.166	0.715 ± 0.261
$t_{½}$ hour	1.27 ± 0.37	1.15 ± 0.41	1.08 ± 0.17	1.34 ± 0.44
V_d Liter	66.91 ± 18.23	59.97 ± 17.65	68.58 ± 21.02	56.73 ± 15.14
Cl Liter/hour	39.06 ± 13.29	38.12 ± 12.64	46.72 ± 16.07	46.72 ± 16.07

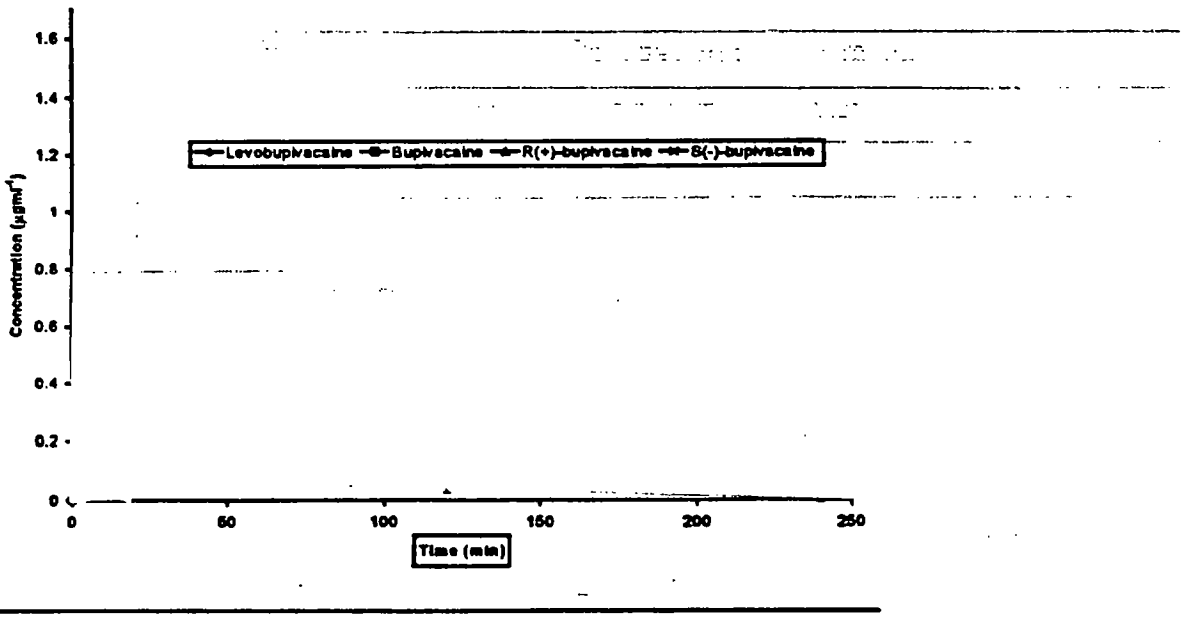

Figure 1. Concentration time profiles (mean ±sd) of levobupivacaine, racemic bupivacaine and R(+)- and S(-)- bupivacaine in healthy male volunteers.

INTRAVENOUS PHARMACOKINETICS

Study Type: Pharmacokinetics
Study Title: A Comparison of The Cardiovascular Effects of Racemic Bupivacaine and S(-)-Bupivacaine In 14 Healthy Volunteers
NDA: 20-997 Submission Date: April 27, 1998 Volume: Protocol:004801
Clinical Investigator: Analytical Investigator:

Single Dose: Yes Cross-over: Yes Other Design: Randomized
Fasted: yes (overnight) Washout-period: 7 days

Subject Breakdown
Normal Yes Young Yes
N= 14 M= 14
Weight Mean 72 kg Range 63-82 kg
Age Mean 29.5 yrs Range 19-40 yrs

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
Bupivacaine	Up to 150 mg	Sterile solution	0.5%	SE130
Levobupivacaine	Up to 150 mg	Sterile Solution	0.5%	4285J

Analytical Methodology

Labeling Claims
None.

Study Objective
To determine if doses of levobupivacaine and bupivacaine produced different degrees of cardiovascular toxicity. In addition, blood samples were taken for pharmacokinetic analysis.

Results and Discussion
Eleven patients were included in the levobupivacaine analysis, and 9 in the bupivacaine analysis. Eventhough the patients could be dosed up to 150 mg, the doses ranged from 22.5 mg to 110 mg for bupivacaine, while the doses ranged from 17.5 to 150 mg for levobupivacaine resulting in a varied dosing history for the different subjects. The pharmacokinetic parameters calculated are presented in Table 1.

No formal statistical analysis was performed on these parameters in Table 1, as it was felt that the limit of detection of the bupivacaine isomers (0.3 µg/mL) would result in inaccurate calculation of pharmacokinetic parameters (for most of the subjects, plasma concentrations could not be reliably quantitated past 2-4 hours). LOQ in majority of studies that used a different assay method was 10 ng/mL. Also data from subjects 003, 004, 011, 012, and 013 (R(+)-bupivacaine) and subjects 003, 004, and 011 (S(-)-bupivacaine) after infusion of racemic bupivacaine were not suitable for simple pharmacokinetic analysis as a result of too few concentrations to analyze after the peak concentration or concentrations which apparently fell and rose again. These subjects were omitted from the mean concentrations when curve fitting was required in the calculation of the pharmacokinetic variable (i.e., other than C_{max} and t_{max}). The mean doses infused were different for levobupivacaine (56.07 mg in a mean time of 5.93 minutes) and bupivacaine (47.9 mg in a mean time of 5.14 minutes). Considering all these factors, the quality of the pharmacokinetic data from these studies is not very strong and as such it would not be used for drawing any strong inferences.

[redacted]

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Table 1. Pharmacokinetic parameters of levobupivacaine, R(+)- bupivacaine and S(-)- bupivacaine after constant rate intravenous infusion (maximum 15 minutes).

Parameter	Levobupivacaine	R(+)- bupivacaine	S(-)- bupivacaine
Dose, mg	56.07 ± 33.96	23.93 ± 12.36	23.93 ± 12.36
C_{max}, µg/mL	2.62 ± 1.11	1.01 ± 0.42	1.24 ± 0.53
t_{max}, minutes	7.50 ± 3.35	8.50 ± 5.96	7.43 ± 3.67
$t_{½}$, minutes	49.92 ± 27.17	81.81 ± 113.28	80.05 ± 85.11
AUC_{inf}, µg minute/mL	109.79 ± 78.74	67.89 ± 60.79	82.23 ± 69.21
Cl, Liter/minute	0.59 ± 0.19	0.55 ± 0.31	0.41 ± 0.18
V_d, Liter	36.78 ± 11.91	32.84 ± 13.01	29.91 ± 6.67

Note: R(+)- and S(-)- bupivacaine was administered as racemic bupivacaine.

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EPIDURAL ANESTHESIA – LABOR

Study Type: Efficacy, Safety, and Pharmacokinetics
Study Title: A Randomized, Multicentre, Double-Blind, Parallel Group Study to Compare the Efficacy, Safety and Kinetics of 0.25% Levobupivacaine (S-Enantiomer) with 0.25% Bupivacaine (Racemic Mixture) in Obstetric Patients Receiving Extradural Analgesia For Labour.
NDA: 20-997 Submission Date: April 27, 1998 Volume: 1.25 Protocol:030276
Clinical Investigators: Analytical Investigator:

Single Dose: Yes Cross-over: No-parallel Other Design: Randomized, double-blind
Subject Breakdown
Patients Yes Young Yes
N= 162 F=162
Weight Mean 76 kg Range 52-105 kg
Age Mean 27 yrs Range 19-37 yrs
Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
Bupivacaine	15 mL	Sterile solution	0.25%	-
Levobupivacaine	15 mL	Sterile Solution	0.25%	2371K & 645005

Analytical Methodology

Labeling Claims
Neither total plasma exposure nor C_{max} differed between the two drugs when compared within studies. These data suggest that Chirocaine and racemic bupivacaine have a similar pharmacokinetic profile.

Results and Discussion
Study 030276 was a Phase III, double-blind, randomized, parallel group study comparing the efficacy, safety and pharmacokinetics of 0.25% levobupivacaine with 0.25% racemic bupivacaine in obstetric patients receiving epidural analgesia during labor. Analgesia was initiated with 10ml (25mg) of study drug with the provision for patients to receive an additional seven bolus injections as top-ups (total dose of 200mg). One hundred and sixty-two patients in total were randomized and samples were collected from 20 patients. Blood samples were collected at 0, 10, 20, 30, 45 and 60 minutes after the first injection of study drug. Concentration time profiles (mean ± SD) are presented in Figure 1 and the pharmacokinetic parameters calculated are presented in Table 1.

The mean C_{max} after the epidural injection of a 25 mg dose of levobupivacaine was 0.206 µg/mL. The mean C_{max} of bupivacaine was slightly lower but similar to that of levobupivacaine. Between R(+)-bupivacaine and S(-)-bupivacaine of racemic bupivacaine, the mean C_{max} of S(-)-bupivacaine was

higher. Since blood samples were collected for up to 1 hour only after administration of study drug, a reliable estimate of the terminal rate constant cannot be obtained and use of $AUC_{0\text{-}60minutes}$ even for gross comparisons is not appropriate.

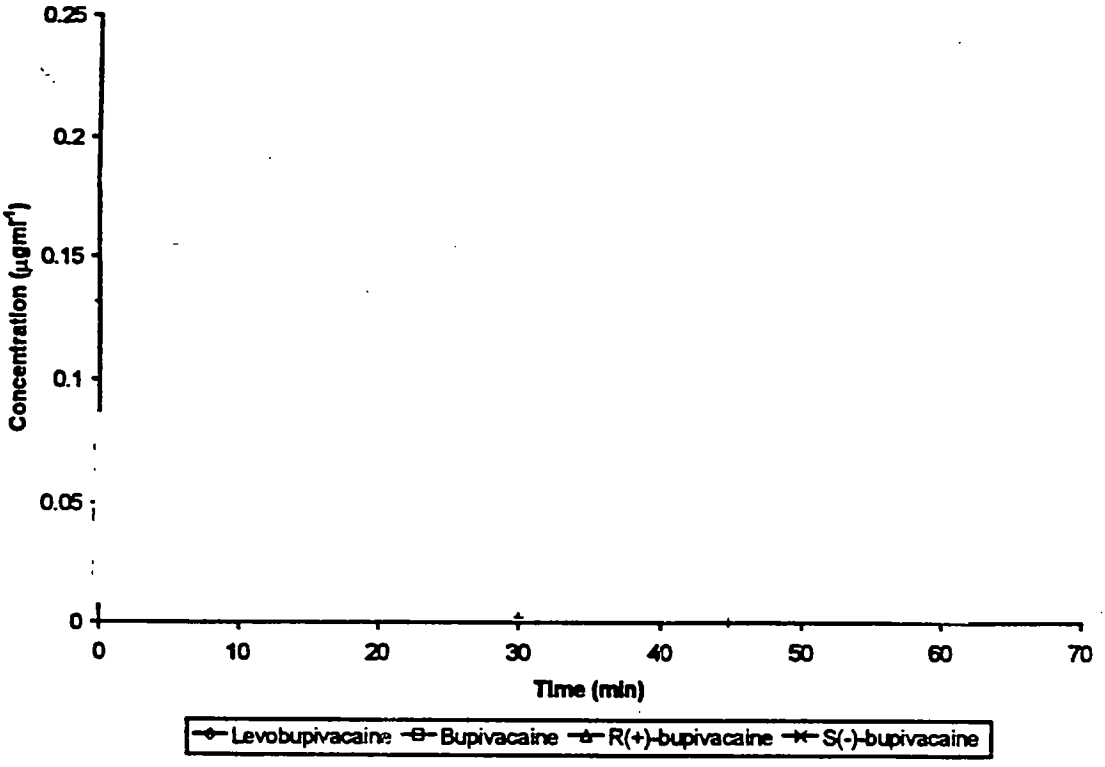

Figure 1. Concentration time profiles (mean ±sd) of levobupivacaine, racemic bupivacaine and R(+)- and S(-)- bupivacaine in patients in labor.

Table 1. Pharmacokinetic parameters of levobupivacaine, racemic bupivacaine, R(+)- bupivacaine and S(-)- bupivacaine in patients in labor.

Parameter	0.25% Levobupivacaine	0.25% Bupivacaine	R(+)- bupivacaine	S(-)- bupivacaine
C_{max} µg/mL	0.206 ± 0.038	0.183 ± 0.076	0.087 ± 0.031	0.103 ± 0.037
t_{max} hour	0.27 ± 0.05	0.27 ± 0.09	0.30 ± 0.14	0.28 ± 0.07
$AUC_{0\text{-}t}$ µg hour/mL	0.132 ± 0.031	0.089 ± 0.061	0.036 ± 0.029	0.051 ± 0.034

EPIDURAL ANESTHESIA – CESAREAN SECTION

Study Type: Efficacy, Safety, and Pharmacokinetics
Study Title: Double-Blind, Randomized, Controlled Trial of 0. 5% Levobupivacaine compared to 0.5% Bupivacaine for Epidural Anesthesia in Patients Undergoing Major Elective Abdominal Surgery.
NDA: 20-997 Submission Date: April 27, 1998 Volume: 1.31 Protocol:CS001
Clinical Investigator: Analytical Investigator:

Single Dose: Yes Cross-over: No-parallel Other Design: Randomized, double-blind
Subject Breakdown
Patients Yes Young No
N= 56 M=24 F=32
Weight Mean 78 kg Range 46-108kg
Age Mean 53 yrs Range 28-80 yrs
Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
Bupivacaine	0.4 mL/kg	Sterile solution	0.5%	-
Levobupivacaine	0.4 mL/kg	Sterile Solution	0.5%	645007

Analytical Methodology

Labeling Claims
None

Results and Discussion

Study CS001 was a Phase III double-blind, randomized, controlled trial comparing the efficacy and safety of 0.5% levobupivacaine with 0.5% bupivacaine in patients undergoing elective Cesarian section performed under epidural anesthesia. Up to 30 mL (total dose of 150 mg) study drug was administered prior to surgery (100-150 mg is recommended in the proposed package insert). Sixty-three patients in total were randomized with samples collected from 18 evaluable patients. The results of the pharmacokinetic analysis are presented in Table 1.

The mean C_{max} after the epidural injection of a 150 mg dose of levobupivacaine was 1.207 µg/mL. The mean C_{max} of bupivacaine was similar but slightly lower than that of levobupivacaine. Between R(+)-bupivacaine and S(-)-bupivacaine of racemic bupivacaine, the mean C_{max} and AUC_{0-24} of S(-)-bupivacaine were higher over those of R(+)-bupivacaine.

Table 1. Pharmacokinetic parameters of levobupivacaine, bupivacaine and the R(+)- and S(-)-enantiomers in patients undergoing elective Caesarian section.

Parameter	0.5% Levobupivacaine	0.5% Bupivacaine	R(+)-bupivacaine	S(-)-bupivacaine
C_{max} µg/mL	1.207 ± 0.388	1.102 ± 0.356	0.505 ± 0.166	0.600 ± 0.190
T_{max} hour	0.49 ± 0.23	0.53 ± 0.27	0.55 ± 0.27	0.45 ± 0.23
AUC_{0-t} µg hour/mL	4.722 ± 1.198	3.846 ± 0.833	1.816 ± 0.398	2.030 ± 0.444

EPIDURAL ANESTHESIA – CESAREAN SECTION

Study Type: Efficacy, Safety, and Pharmacokinetics
Study Title: A Double-Blind, Randomized, Controlled Trial of 0.5% Levobupivacaine compared to 0.5% Bupivacaine for Extradural Anesthesia in Patients Undergoing Elective Cesarean Section.
NDA: 20-997 Submission Date: April 27, 1998 Volume: 1.29 Protocol:030632
Clinical Investigator: Analytical Investigator:

Single Dose: Yes Cross-over: No-parallel Other Design: Randomized, double-blind
Subject Breakdown
Patients Yes Young Yes
N= 67 F=67
Weight Mean 77 kg Range 50-109kg
Age Mean 30 yrs Range 18-40 yrs
Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
Bupivacaine	25 mL	Sterile solution	0.5%	XD219, XE22
Levobupivacaine	25 mL	Sterile Solution	0.5%	645006

Analytical Methodology

Labeling Claims
None

Results and Discussion

Study 030632 was a Phase III double-blind, randomized, controlled trial comparing the efficacy and safety of 0.5% levobupivacaine with 0.5% bupivacaine in patients undergoing elective Caesarian section performed under epidural anesthesia. Epidural blocks were initiated with 25 mL of study drug (125 mg) with the option of an additional 5 mL (total dose 150 mg) prior to the start of surgery (100-150 mg is recommended in the proposed package insert). Sixty-seven patients in total were randomized to the study, blood samples from 19 patients were evaluated for pharmacokinetic analysis. The results of the pharmacokinetic analysis are presented in Table 1, and the mean concentration-time profiles are presented in Figure 1.

The mean C_{max} after the epidural injection of a 150 mg dose of levobupivacaine was 1.137 µg/mL. The mean C_{max} of bupivacaine was similar to that of levobupivacaine. Between R(+)-bupivacaine and S(-)-bupivacaine of racemic bupivacaine, the mean C_{max} and AUC_{0-8} of S(-)-bupivacaine were higher.

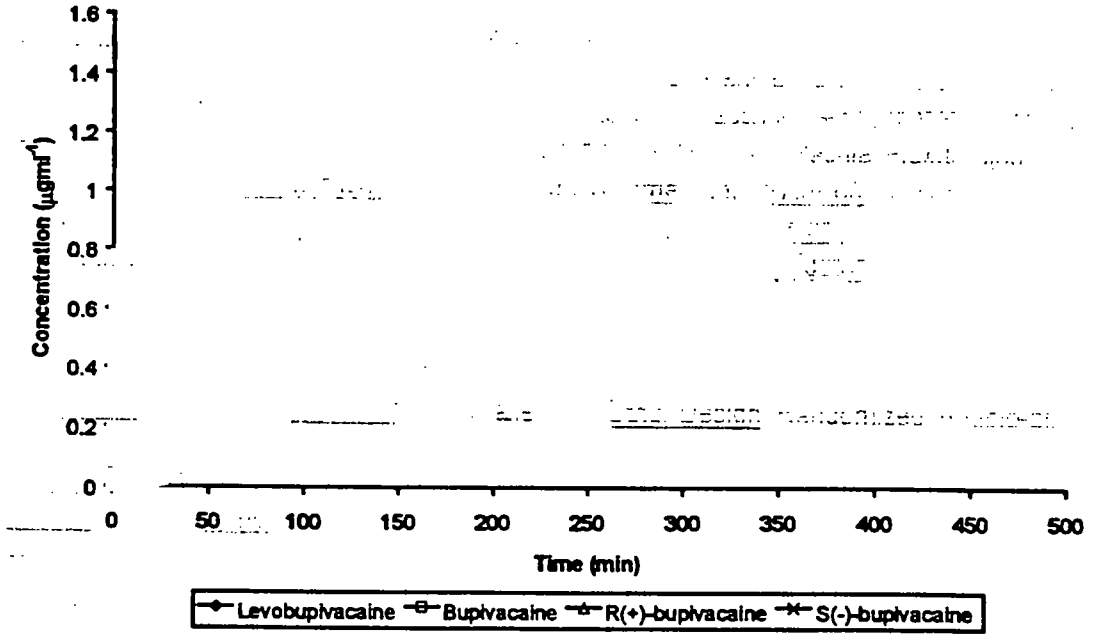

Figure 1. Concentration time profiles (mean ±sd) of levobupivacaine, racemic bupivacaine and R(+)- and S(-)- bupivacaine in patients undergoing elective Caesarian section.

Table 1. Pharmacokinetic parameters (mean ±sd) of 0.5% levobupivacaine, 0.5% bupivacaine racemate, R(+)- bupivacaine and S(-)- bupivacaine in patients undergoing elective Caesarian section.

Parameter	0.5% Levobupivacaine	0.5% Bupivacaine	R(+)-bupivacaine	S(-)-bupivacaine
C_{max} µg/mL	1.137 ± 0.321	1.135 ± 0.402	0.535 ± 0.175	0.601 ± 0.229
t_{max} hour	0.56 ± 0.12	0.55 ± 0.19	0.55 ± 0.19	0.52 ± 0.18
AUC_{0-8} µg hour/mL	3.289 ± 0.774	3.041 ± 0.663	1.470 ± 0.349	1.571 ± 0.325

EPIDURAL ANESTHESIA –ELECTIVE LOWER LIMB SURGERY

Study Type: Efficacy, Safety, and Pharmacokinetics
Study Title: A Randomized, Multicentre, Double-Blind, Parallel Group Study to Evaluate the Dose Response, Safety and Kinetics of 15 mL of 0.5% Levobupivacaine (S-Enantiomer) with 15 mL of 0.5% Bupivacaine (Racemic Mixture) in Patients Undergoing Elective Surgery Under Epidural Anesthesia.
NDA: 20-997 Submission Date: April 27, 1998 Volume: 1.34 Protocol:006175
Clinical Investigators: Analytical Investigator:

Single Dose: Yes Cross-over: No-parallel Other Design: Randomized, double-blind

Subject Breakdown
Patients Yes Young No
N= 96 M=35 F=61
Weight Mean 72 kg Range 45-128 kg
Age Mean 47 yrs Range 19-80 yrs

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
Bupivacaine	15 mL	Sterile solution	0.5%	-
Levobupivacaine	15 mL	Sterile Solution	0.75%	2373K
Levobupivacaine	15 mL	Sterile Solution	0.5%	2372K

Analytical Methodology

Labeling Claims
Neither total plasma exposure nor C_{max} differed between the two drugs when compared within studies. These data suggest that Chirocaine and racemic bupivacaine have a similar pharmacokinetic profile.

Results and Discussion
Study 006175 was a Phase III double-blind, randomized, parallel group trial comparing the efficacy, plasma concentrations and safety profiles of two different concentrations of levobupivacaine (0.5% and 0.75%) with 0.5% racemic bupivacaine in patients undergoing elective lower limb vascular surgery or arthroscopy performed under epidural anesthesia. Patients were administered 15 mL of study drug (75 to 112.5mg). Ninety-six patients were recruited into the study from which samples from 26 patients were evaluable for the pharmacokinetic analysis. Blood samples were taken pre-dose, and at 10, 20, 30, 45 minutes and at 1, 1.5, 2, 4, 6, 8, 10 and 24 hour after injection of the study drug. Figure 1 shows

the concentration time profiles (mean ±sd) for this study and Table 1 shows the pharmacokinetic parameters calculated.

Between 0.5% and 0.75% levobupivacaine (75 mg and 112.5 mg), the mean C_{max} and AUC_{0-24} of levobupivacaine were approximately dose-proportional (the values were about 1.4 fold higher for 0.75% levobupivacaine over those of 0.5% levobupivacaine). Between 0.5% levobupivacaine and 0.5% bupivacaine, the mean C_{max} after the epidural injection of a 75 mg dose of levobupivacaine was 0.582 µg/mL. The mean C_{max} of bupivacaine was similar but slightly lower than that of levobupivacaine. Between R(+)-bupivacaine and S(-)-bupivacaine of racemic bupivacaine, the mean C_{max} and AUC_{0-24} of S(-)-bupivacaine were higher over those of R(+)-bupivacaine.

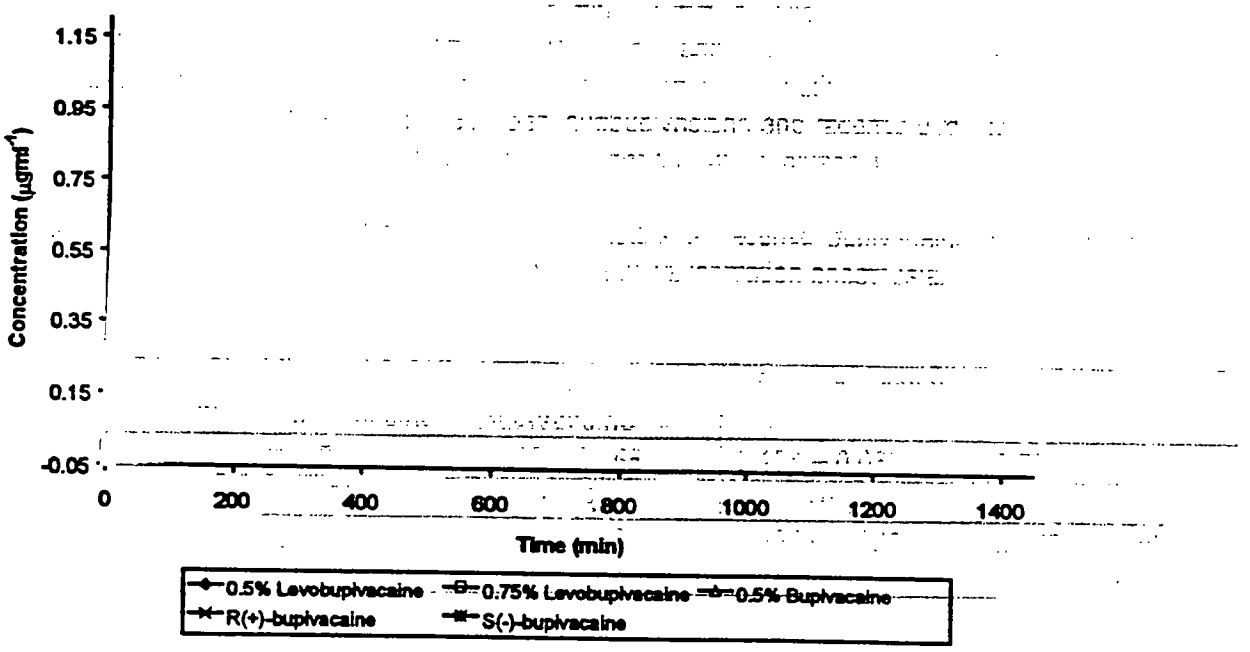

Figure 1. Concentration time profiles of 0.5% and 0.75% levobupivacaine, R(+)- and S(-) enantiomers, and 0.5% bupivacaine in patients undergoing major abdominal surgery.

Table 1. Pharmacokinetic parameters of 0.5% and 0.75% levobupivacaine, 0.5% bupivacaine and the R(+)- and S(-)- enantiomers in patients undergoing elective surgery under epidural anesthesia.

Parameter	0.5% Levobupivacaine	0.75% Levobupivacaine	0.5% Bupivacaine	R(+)-bupivacaine	S(-)-bupivacaine
C_{max} µg/mL	0.582 ± 0.25	0.811 ± 0.341	0.414 ± 0.162	0.188 ± 0.075	0.227 ± 0.088
t_{max} hour	0.52 ± 0.14	0.44 ± 0.19	0.36 ± 0.08	0.36 ± 0.08	0.44 ± 0.29
AUC_{0-t} µg hour/mL	3.561 ± 1.483	4.93 ± 1.846	2.044 ± 1.190	0.707 ± 0.437	1.212 ± 0.730

EPIDURAL ANESTHESIA – MAJOR ELECTIVE ABDOMINAL SURGERY

Study Type: Efficacy, Safety, and Pharmacokinetics
Study Title: Double-Blind, Randomized, Controlled Trial of 0.75 Levobupivacaine compared to 0.75% Bupivacaine for Epidural Anesthesia in Patients Undergoing Major Elective Abdominal Surgery.
NDA: 20-997 Submission Date: April 27, 1998 Volume: 1.37 Protocol:CS005
Clinical Investigator: Analytical Investigator:

Single Dose: Yes Cross-over: No-parallel Other Design: Randomized, double-blind

Subject Breakdown
Patients Yes Young No
N= 56 M=24 F=32
Weight Mean 78 kg Range 46-108kg
Age Mean 53 yrs Range 28-80 yrs

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
Bupivacaine	0.4 mL/kg	Sterile solution	0.75%	-
Levobupivacaine	0.4 mL/kg	Sterile Solution	0.75%	645007

Analytical Methodology

Labeling Claims
None

Results and Discussion

Study CS 005 was a Phase III double-blind, randomized controlled trial comparing the efficacy and safety of 0.75% levobupivacaine with 0.75% bupivacaine in patients undergoing major abdominal surgery. Each patient received 20ml of study drug (150mg) prior to surgery, with allowance for top-ups. Twenty-two patients had multiple blood samples withdrawn (at 0, 15, 30, 45 minutes and 1, 2, 4, 6, 8 and 10 hour's post dose). Variability in the number and timing of the top-up dosages given meant that the pharmacokinetic parameters for this group could not be calculated with confidence. The mean and standard deviation concentration time profile is presented in Figure 1 to emphasize the variability encountered.

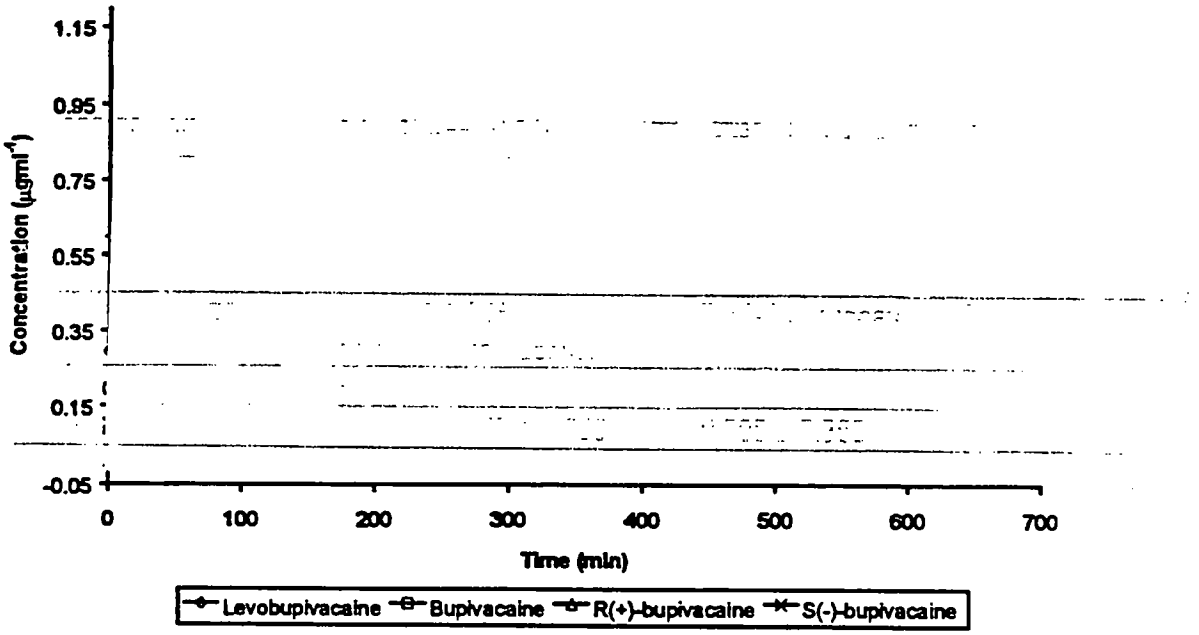

Figure 1. Concentration time profiles of 0.75% levobupivacaine, 0.75% bupivacaine and the R(+)- and S(-)- enantiomers in patients undergoing major abdominal surgery.

BRACHIAL PLEXUS BLOCK

Study Type: Efficacy, Safety, and Pharmacokinetics
Study Title: A Randomized, Multicentre, Double-Blind, Parallel Group Study To Evaluate the Dose Response, Kinetics and Safety of 0.25 and 0.5% Levobupivacaine (S-Enantiomer) with 0.5% Bupivacaine (Racemic Mixture) in Patients Undergoing Elective Surgery Under Brachial Plexus Block.
NDA: 20-997 Submission Date: April 27, 1998 Volume: 1.39 Protocol:006154
Clinical Investigator: [redacted] Analytical Investigator: [redacted]

Single Dose: Yes Cross-over: No-parallel Other Design: Randomized, double-blind

Subject Breakdown

Patients Yes	Young No	
N= 76	M=49	F=26
Weight	Mean 71kg	Range 38-100kg
Age	Mean 54yrs	Range 19-84 yrs

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
Bupivacaine	0.4 mL/kg	Sterile solution	0.5%	2371K
Levobupivacaine	0.4 mL/kg	Sterile Solution	0.25%	2372K
Levobupivacaine	0.4 mL/kg	Sterile Solution	0.5%	2372K

Analytical Methodology

[redacted]

Labeling Claims
Neither total plasma exposure nor Cmax differed between the two drugs when compared within studies. These data suggest that chirocaine and racemic bupivacaine have a similar pharmacokinetic profile.

Results and Discussion
This was a Phase III double-blind, randomized, parallel group trial comparing the efficacy, plasma concentrations, and safety profiles of two different concentrations of levobupivacaine (0.25% and 0.5%) with 0.5% racemic bupivacaine in patients undergoing elective hand surgery performed under local anesthesia with a supraclavicular brachial plexus block. Each patient received a dose of 0.4mL/kg.

Seventy-six patients in total were recruited into this study of which samples were collected from 30 evaluable patients. Blood samples were collected pre-dose, and at 10, 20, 30, 45min and 1, 1.5, 2, 4, 6, 8, 10 and 24 hours after injection of study drug. Plasma concentration time curves (mean ±sd) are presented in Figure 1 and a summary of the pharmacokinetic variables in Table 1.

Between 0.25% and 0.5% levobupivacaine, the mean C_{max} and AUC_{0-24} of levobupivacaine were approximately dose-proportional (the values were about 2 fold and 1.8 fold higher, respectively, for 0.25% levobupivacaine over those of 0.5% levobupivacaine). The mean C_{max} and AUC_{0-24} of 0.5% bupivacaine were similar but higher than those of 0.5% levobupivacaine. Between R(+)-bupivacaine and S(-)-bupivacaine of racemic bupivacaine, the mean C_{max} and AUC_{0-24} of S(-)-bupivacaine were higher over those of R(+)-bupivacaine.

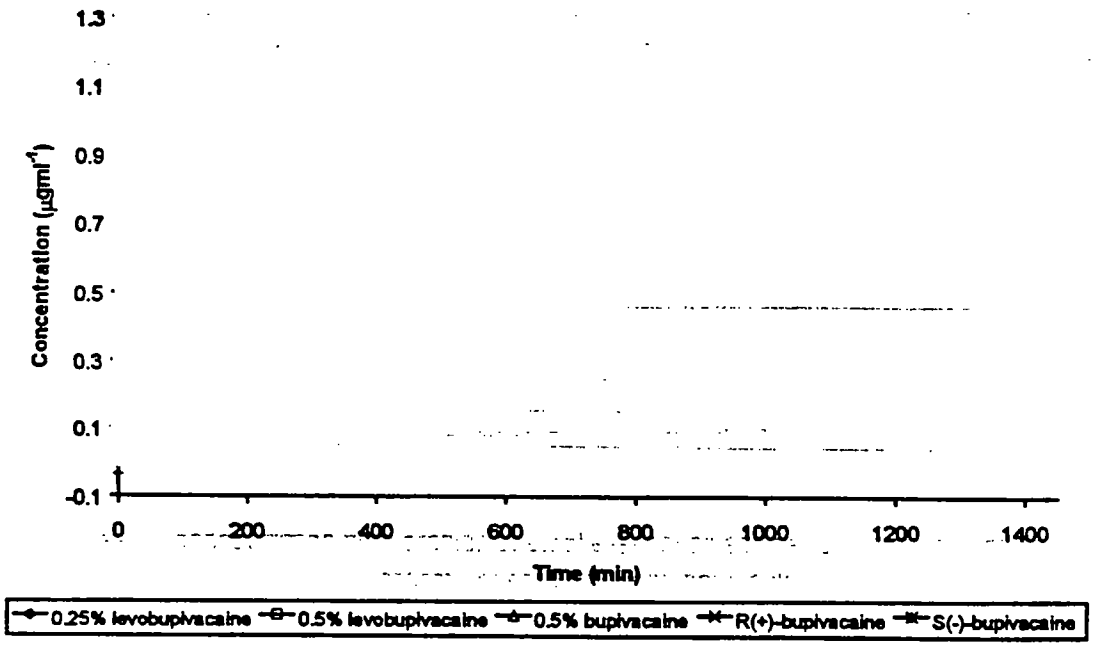

Figure 1. Concentration time profiles of 0.25% and 0.5% levobupivacaine, 0.5% bupivacaine and R(+)- and S(-)- enantiomers in patients undergoing brachial plexus block.

Table 1. Pharmacokinetic parameters of 0.25 and 0.5% levobupivacaine, 0.5% bupivacaine and the R(+)- and S(-)- enantiomers in patients undergoing brachial plexus block.

	0.25% levobupivacaine	0.5% levobupivacaine	0.5% bupivacaine	bupivacaine R(+)-enantiomer	bupivacaine S(-)- enantiomer
C_{max} (µg/mL)	0.474 ± 0.189	0.961 ± 0.282	1.029 ± 0.307	0.465 ± 0.139	0.568 ± 0.139
t_{max} (hour)	0.5 ± 0.16	0.7 ± 0.34	0.7 ± 0.23	0.7 ± 0.26	0.68 ± 0.23
$AUC_{(0-t)}$ (hour µg/mL)	2.999 ± 0.767	5.311 ± 1.662	6.832 ± 3.925	2.952 ± 1.677	3.881 ± 2.264
$T_{½}$ (hour)	19.7 ± 22.7	19.5 ± 22.8	12.8 ± 7.9	13.6 ± 7.6	12.6 ± 7.4

INFILTRATION ANESTHESIA

Study Type: Efficacy, Safety, and Pharmacokinetics.
Study Title: A Randomized, Single-Centre, Double-Blind, Parallel Group Study to Compare Efficacy, Safety and Pharmacokinetics of 0.25% Levobupivacaine (S-Enantiomer) and 0.25% Bupivacaine (Racemic Mixture) Given as Infiltration Anesthesia in Patients Undergoing Elective Inguinal Hernia Repair.
NDA: 20-997 Submission Date: April 27, 1998 Volume: 1.41 Protocol:030428
Clinical Investigator: Analytical Investigator:

Single Dose: Yes Cross-over: No-parallel Other Design: Randomized, double-blind

Subject Breakdown
Patients Yes Young No
N= 66 M=66
Weight Mean 75kg Range 50-100 kg
Age Mean 57yrs Range 30-79 yrs

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
Bupivacaine	Up to 150 mg	Sterile solution	0.25%	XE86
Levobupivacaine	Up to 150 mg	Sterile Solution	0.25%	645005

Analytical Methodology

Labeling Claims
None

Results and Discussion

Study 030428 was a Phase III double-blind, randomized, parallel group trial comparing the efficacy, safety and pharmacokinetics of 0.25% levobupivacaine with 0.25% bupivacaine administered by infiltration anesthesia in patients undergoing inguinal hernia surgery. Anesthesia was initiated with 50 mL of study drug (125 mg); an additional 10mL could be administered if required (total dose of up to that recommended in the package insert-150mg). Twenty patients were recruited for pharmacokinetic evaluation, of which 17 were evaluable (9 levobupivacaine, 8 bupivacaine). The summary of the pharmacokinetic parameters is presented in Table 1.

Since blood samples were collected for up to 4 hours only after administration of study drug, a reliable estimate of the terminal rate constant cannot be obtained. Also, each of the subsequent doses were given at different times to the patient implying that the peak and time to peak concentrations and AUC_{0-t} values can only be used for making gross comparisons. The C_{max} and AUC_{0-t} were higher for S(-)-bupivacaine over R(+)-bupivacaine after the administration of 0.25% racemic bupivacaine following the general trend seen in other studies. Between levobupivacaine and racemic bupivacaine, the C_{max} was lower and the AUC was similar for levobupivacaine compared with bupivacaine.

Table 1. A summary of the pharmacokinetic parameters of racemic bupivacaine, the R(+)- and S(-)-enantiomers, and levobupivacaine after ilioinguinal/infiltration anesthesia.

Parameter	0.25% Levobupivacaine	0.25% Bupivacaine	R(+)-bupivacaine	S(-)-bupivacaine
C_{max} µg/mL	0.381 ± 0.156	0.418 ± 0.155	0.184 ± 0.065	0.234 ± 0.090
t_{max} hour	0.56 ± 0.52	0.32 ± 0.25	0.29 ± 0.14	0.32 ± 0.25
AUC_{0-t} µg hour/mL	1.128 ± 0.559	1.090 ± 0.395	0.464 ± 0.160	0.626 ± 0.235

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ON ORIGINAL

INFILTRATION ANESTHESIA

Study Type: Efficacy, Safety, and Pharmacokinetics.
Study Title: A Randomized, Single-Centre, Double-Blind, Parallel Group Study to Compare Efficacy, Safety and Pharmacokinetics of 0.25% Levobupivacaine with 0.25% Bupivacaine (Racemic Mixture) Given as Infiltration Anesthesia in Patients Undergoing Elective Inguinal Hernia Repair.
NDA: 20-997 Submission Date: April 27, 1998 Volume: 1.43 Protocol:030721
Clinical Investigator: Analytical Investigator:

Single Dose: Yes Cross-over: No-parallel Other Design: Randomized, double-blind

Subject Breakdown
Patients Yes Young No
N= 69 M=69
Weight Mean 78kg Range 59-112 kg
Age Mean 58 yrs Range 28-88 yrs

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
Bupivacaine	Up to 150 mg	Sterile solution	0.25%	XE86
Levobupivacaine	Up to 150 mg	Sterile Solution	0.25%	645005

Analytical Methodology

Labeling Claims
None

Results and Discussion

Study 030721 was a Phase III double-blind, randomized, parallel group trial comparing the efficacy, safety and pharmacokinetics of 0.25% levobupivacaine with 0.25% bupivacaine when used for ilioinguinal/infiltration anesthesia in patients undergoing elective inguinal hernia repair. Anesthesia was initiated with 50 mL of study drug (125mg), an additional 10ml could be administered during the course of surgery (total dose up to 150mg). The additional amount given varied between 1 and 10 mL and was given at varying times after the initial administration of the drug, sometimes even in different stages. Therefore, variability in the dosage regimen meant that calculation of pharmacokinetic parameters could not be

conducted on the 21 patients who had pharmacokinetic samples taken. Mean and standard deviations for C_{max} and t_{max} determined in this study are presented in Table 1 for illustrative purposes only.

Table 1. Mean and standard deviation of C_{max} and t_{max} calculated after ilioinguinal/infiltration anesthesia for inguinal hernia repair.

Parameter	0.25% Levobupivacaine	0.25% Bupivacaine	R(+)- bupivacaine	S(-)- bupivacaine
C_{max} µg/mL	0.640 ± 0.248	0.599 ± 0.328	0.272 ± 0.158	0.327 ± 0.170
t_{max} hour	0.591 ± 0.231	0.658 ± 0.380	0.608 ± 0.363	0.658 ± 0.380

PERIBULBAR BLOCK

Study Type: Efficacy and Safety
Study Title: A study to compare the efficacy and safety of 0.75% levobupivacaine with 0.75% bupivacaine in peribulbar block for ophthalmic anterior segment surgery.
NDA: 20-997 Submission Date: April 27, 1998 Volume: 1.45 Protocol:030737
Clinical Investigator: Analytical Investigator:

Single Dose: Yes Cross-over: No-parallel Other Design: Randomized, double-blind

Subject Breakdown
Patients Yes Young No
N= 60 M=20 F=40
Weight Mean 70kg Range 45-106 kg
Age Mean 77 yrs Range 56-90 yrs

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
Bupivacaine	37.5 mg	Sterile solution	0.75%	XM63
Levobupivacaine	37.5 mg	Sterile Solution	0.75%	645007

Analytical Methodology

Labeling Claims
None

Results and Discussion

This was a Phase III double-blind, randomized, parallel group trial comparing the efficacy and safety of 0.75% levobupivacaine with 0.75% bupivacaine in sixty (60) patients undergoing elective ophthalmic anterior segment surgery performed under peribulbar block. Ophthalmic block was achieved with a total dose of 37.5 mg (sponsor's proposed dosage recommendation is 37.5 – 112.5 mg). Pharmacokinetics were determined from twenty (20) of the sixty (60) patients. Since blood samples were collected for up to 4 hours after administration of study drug and a reliable estimate of the terminal rate constant cannot be obtained, the emphasis is on the peak and time to peak concentrations only (AUC_{0-4} is to be used for gross comparisons). The mean concentration time profiles are shown in Figure 1 and a summary of the pharmacokinetic parameters is presented in Table 1. For all four entities, at the 45 minute time point, there is an uncharacteristic dip in the concentrations. It is not clear if this is a characteristic of

this route of administration or if it is an artifact, the cause for this artifact is unknown. The mean C_{max} was 0.41 µg/mL after the administration of a 37.5 mg dose of 0.75% levobupivacaine. Between levobupivacaine and racemic bupivacaine, C_{max} and AUC_{0-t} of levobupivacaine were 147% and 125% of that of racemic bupivacaine. As was found in other studies, the C_{max} and AUC_{0-t} were higher for S(-)-bupivacaine over R(+)-bupivacaine after the administration of 0.75% racemic bupivacaine.

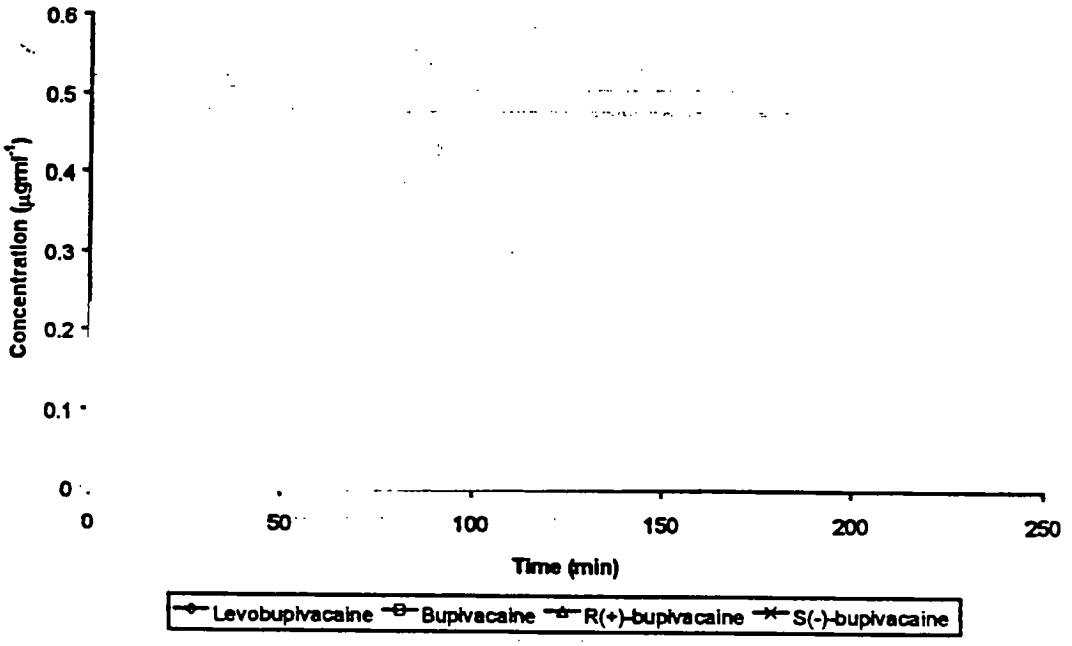

Figure 1. Plasma concentration time profiles of 0.75% levobupivacaine, 0.75% bupivacaine and the R(+)- and S(-) enantiomers in patients undergoing peribulbar block.

Table 1. A summary of the pharmacokinetic parameters of levobupivacaine, bupivacaine and the R(+)- and S(-)- enantiomers after peribulbar block for ophthalmic surgery.

Parameter	0.75% Levobupivacaine	0.75% Bupivacaine	R(+)- bupivacaine	S(-)- bupivacaine
C_{max} µg/mL	0.410 ± 0.145	0.281 ± 0.096	0.122 ± 0.043	0.159 ± 0.053
t_{max} hour	0.32 ± 0.17	0.36 ± 0.25	0.36 ± 0.25	0.43 ± 0.32
AUC_{0-t} µg hour/mL	0.548 ± 0.128	0.439 ± 0.120	0.185 ± 0.050	0.254 ± 0.071

APPENDIX II

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