CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20997

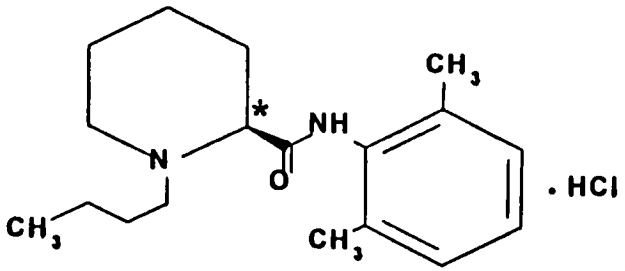
FINAL PRINTED LABELING

CHIROCAINE®(Levobupivacaine Injection)

DESCRIPTION

Chirocaine (levobupivacaine injection) contains a single enantiomer of bupivacaine hydrochloride which is chemically described as (S)-1-butyl-2-piperidylformo-2', 6'-xylidide hydrochloride and it is related chemically and pharmacologically to the amino amide class of local anesthetics.

Levobupivacaine hydrochloride, the S-enantiomer of bupivacaine, is a white crystalline powder with a molecular formula of $C_{18}H_{28}N_2O$. HCl, a molecular weight of 324.9, and with the following structural formula:



* - indicates the chiral center

The solubility of levobupivacaine hydrochloride in water is about 100 mg per mL at 20°C, the partition coefficient (oleyl alcohol/water) is 1624 and the pKa is 8.09. The pKa of levobupivacaine hydrochloride is the same as that of bupivacaine hydrochloride and the partition coefficient is very similar to that of bupivacaine hydrochloride (1565).

Chirocaine is a sterile, non-pyrogenic, colorless solution (pH 4.0-6.5) containing levobupivacaine hydrochloride equivalent to 2.5 mg/mL, 5.0 mg/mL, and 7.5 mg/mL of levobupivacaine, sodium chloride for isotonicity, and Water for Injection. Sodium hydroxide and/or hydrochloric acid may have been added to adjust pH. Chirocaine is preservative free and is available in 10 mL and 30 mL single dose vials.

CLINICAL PHARMACOLOGY

Mechanism of Action

Chirocaine is a member of the amino amide class of local anesthetics. Local anesthetics block the generation and the conduction of nerve impulses by increasing the threshold for electrical excitation in the nerve, by slowing propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: 1) pain, 2) temperature, 3) touch, 4) proprioception and 5) skeletal muscle tone.

Pharmacokinetics

Table 1. Pharmacokinetic parameter values 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

After IV infusion of equivalent doses of levobupivacaine and bupivacaine, the mean clearance, volume of distribution, and terminal half-life values of levobupivacaine and bupivacaine were similar. No detectable levels of R (+)-bupivacaine were found after the administration of levobupivacaine.

A comparison of the estimates for plasma AUC and C_{max} between Chirocaine and bupivacaine in two Phase III clinical trials involving short duration administration of either agent found that neither total plasma exposure or C_{max} differed between the two drugs when compared within studies. Between study values differed somewhat, likely due to differences in the injection sites, volume, and total dose administered in each of the studies. These data suggest that Chirocaine and bupivacaine have a similar pharmacokinetic profile. Pharmacokinetic data from two Phase III studies are presented below:

Table 2. Pharmacokinetic parameter values of levobupivacaine and bupivacaine in patients administered the respective drugs epidurally and for brachial plexus block.

Route	**Epidural**			**Brachial Plexus Block**		
	Levo-bupivacaine		**Bupivacaine**	**Levo-bupivacaine**		**Bupivacaine**
Concentration (%)	**0.50**	**0.75**	**0.50**	**0.25**	**0.50**	**0.50**
Dose received	**75mg**	**112.5mg**	**75mg**	**1 mg/kg**	**2 mg/kg**	**2 mg/kg**
n	9	9	8	10	10	9
C_{max} (μg/mL)	0.582	0.811	0.414	0.474	0.961	1.029
T_{max} (h)	0.52	0.44	0.36	0.50	0.71	0.68
$AUC_{(0-t)}$ (μg.h/mL)	3.561	4.930	2.044	2.999	5.311	6.832

Between 0.5% and 0.75% levobupivacaine given epidurally at doses of 75 mg and 112.5 mg respectively, the mean C_{max} and AUC_{0-24} of levobupivacaine were approximately dose-proportional. Similarly, between 0.25% and 0.5% levobupivacaine used for brachial plexus block at doses of 1 mg/kg and 2 mg/kg respectively, the mean C_{max} and AUC_{0-24} of levobupivacaine were approximately dose-proportional.

Absorption

The plasma concentration of levobupivacaine following therapeutic administration depends on dose and also on route of administration, because absorption from the site of administration is affected by the vascularity of the tissue. Peak levels in blood were reached approximately 30 minutes after epidural administration, and doses up to 150 mg resulted in mean C_{max} levels of up to 1.2 μg/mL.

Distribution

Plasma protein binding of levobupivacaine evaluated *in vitro* was found to be >97% at concentrations between 0.1 and 1 μg/mL. The association of levobupivacaine with human blood cells was very low (0-2%) over the concentration range 0.01-1 μg/mL and increased to 32% at 10 μg/mL. The volume of distribution of levobupivacaine after intravenous administration was 67 liters.

Metabolism

Levobupivacaine is extensively metabolized with no unchanged levobupivacaine detected in urine or feces. *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. *In vivo*, the 3-hydroxy levobupivacaine appears to undergo further transformation to glucuronide and sulfate conjugates. Metabolic inversion of levobupivacaine to R(+)-bupivacaine was not evident both *in vitro* and *in vivo*.

Elimination

Following intravenous administration, 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. The mean clearance and terminal half-life of levobupivacaine after intravenous infusion were 39 liters/hour and 1.3 hours, respectively.

Special Populations

Elderly: The limited data available indicate that while there are some differences in T_{max}, C_{max} and AUC with regards to age (between age groups of <65, 65-75, and >75 years), these differences are small and vary depending on the site of administration.

Gender: The small number of subjects in either of the male and female groups and the different routes of administration (data could not be pooled) in the different studies did not permit the assessment of gender differences in the pharmacokinetics of levobupivacaine.

Pediatrics: No pharmacokinetic data of levobupivacaine are available in the pediatric population.

Maternal/Fetal ratio: The ratio of umbilical venous and maternal concentration of levobupivacaine ranged from 0.252 - 0.303 after the epidural administration of levobupivacaine for cesarean section. These are within the range normally seen for bupivacaine.

*Nursing Mothers:*It is known that some local anesthetic drugs are excreted in human milk and caution should be exercised when they are administered to a nursing woman. The excretion of levobupivacaine or its metabolites in human milk has not been studied (see PRECAUTIONS).

Renal failure:No special studies were conducted in renal failure patients. Unchanged levobupivacaine is not excreted in the urine. Although there is no evidence that levobupivacaine accumulates in patients with renal failure, some of its metabolites may accumulate because they are primarily excreted by the kidney.

Hepatic Failure: No special studies were conducted in hepatic failure patients. Levobupivacaine is eliminated primarily by hepatic metabolism and changes in hepatic function may have significant consequences. Levobupivacaine should be used with caution in patients with severe hepatic disease, and repeated doses may need to be reduced due to delayed elimination.

Drug-Drug interactions: *In vitro* studies showed that morphine, fentanyl, clonidine, and sufentanil are not likely to have an inhibitory effect on the oxidative metabolism of levobupivacaine. However, none of these tested compounds was an inhibitor of the CYP3A4 or CYP1A2 isoforms. Although no clinical studies have been conducted, it is likely that the metabolism of levobupivacaine may be affected by the known CYP3A4 inducers (such as phenytoin, phenobarbital, rifampin), CYP3A4 inhibitors (azole antimycotics e.g., ketoconazole; certain protease inhibitors e.g., ritanovir; macrolide antibiotics e.g., erythromycin; and calcium channel antagonists e.g., verapamil), CYP1A2 inducers (omeprazole) and CYP1A2 inhibitors (furafylline and clarithromycin).

Relative Potency

The relative potency of Chirocaine compared to bupivacaine has not been established.

Pharmacodynamics

Chirocaine can be expected to share the pharmacodynamic properties of other local anesthetics. Systemic absorption of local anesthetics can produce effects on the central nervous and cardiovascular systems. At blood concentrations achieved with therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance have been reported. Toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in death. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central nervous system stimulation is usually manifested as restlessness, tremors, and shivering, progressing to convulsions. Ultimately central nervous system depression may progress to coma and cardio-respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited stage.

In nonclinical pharmacology studies comparing Chirocaine and bupivacaine in animal species, both the CNS and the cardiac toxicity of Chirocaine were less than that of bupivacaine. Arrhythmogenic effects were seen in animals at higher doses of Chirocaine than bupivacaine. Animal data comparing the difficulty of resuscitation from levobupivacaine- and bupivacaine-induced arrhythmia are not available. Central nervous system toxicity occurred with both drugs at lower doses and at lower plasma concentrations than those doses and plasma concentrations associated with cardiotoxicity.

In two intravenous infusion studies in conscious sheep, the convulsive doses of levobupivacaine were found to be significantly higher than for bupivacaine. Following repeated intravenous bolus administration mean (± SD) convulsive doses for levobupivacaine and bupivacaine were 9.7 (7.9) mg/kg and 6.1 (3.4) mg/kg respectively. The associated median total serum concentrations were 3.2 μg/ml and 1.6 μg/ml. In a second study following a 3 minute intravenous infusion the mean convulsant dose (95% CI) for levobupivacaine was 101 mg (87-116 mg) and for bupivacaine 79 mg (72-87 mg).

A study in human volunteers was designed to assess the effects of Chirocaine and bupivacaine on the EEG following an intravenous dose (40 mg) that was predicted to be below the threshold to cause CNS symptoms. In this study, levobupivacaine decreased high alpha power in the parietal, temporal and occipital regions, but to a lesser extent than bupivacaine. Levobupivacaine had no effect on high alpha power in the frontal and central regions, nor did it produce the increase in theta power observed at some electrodes following bupivacaine.

In another study, 14 subjects received Chirocaine or bupivacaine infusions intravenously until significant CNS symptoms occurred (occurrence of numbness of the tongue, light-headedness, tinnitus, dizziness, blurred vision, or muscle twitching. The mean dose at which CNS symptoms occurred was 56 mg (range 17.5-150 mg) for Chirocaine and 48 mg (range 22.5-110 mg) for bupivacaine; this difference did not reach statistical significance. The primary endpoints of the study were cardiac contractility and standard electrocardiographic parameters. Although some differences were seen between treatments, the clinical relevance of these is unknown.

CLINICAL TRIALS

The clinical trial program included 1220 patients and subjects who received Chirocaine in 31 clinical trials. Chirocaine has been studied as a local anesthetic in adults administered as an epidural block for surgical cases, including cesarean section; in peripheral neural blockade; and for post-operative pain control. Although relative potency has not been established, clinical trials have demonstrated that Chirocaine and bupivacaine exhibit similar anesthetic effects (see CLINICAL PHARMACOLOGY; Relative Potency).

Central Administration

Epidural Administration in Cesarean Section

In one study, Chirocaine and bupivacaine, 0.50%, were evaluated as an epidural block in 62 patients undergoing cesarean section in a randomized, double-blind comparative trial. The mean (± s.d.) time to sensory block measured at T4 to T6 was 10 ± 8 minutes for Chirocaine and 6± 4 minutes for bupivacaine The mean duration of sensory and motor block was 8 ± 1 and 4 ± 1 hours for Chirocaineand 7 ± 1 and 4 ± 1 hours for bupivacaine, respectively. Ninety-four percent of patients receiving Chirocaine and 100 % of patients receiving bupivacaine achieved a block adequate for surgery. In a second bupivacaine-controlled cesarean section study involving 62 patients, the mean time to onset of T4 to T6 sensory block for Chirocaine and bupivacaine was 10 ± 7 minutes and 9 ± 7 minutes, respectively, with 94% of Chirocaine patients and 91% of bupivacaine patients achieving a bilateral block adequate for surgery. The mean time to complete regression of sensory block was 8 ± 2 hours for both treatments.

Epidural Administration During Labor and Delivery

Chirocaine 0.25% was evaluated as intermittent injections via an epidural catheter in 68 patients during labor in a randomized double-blind comparative trial to bupivacaine 0.25%. The median duration of pain relief in the subset of patients receiving 0.25% Chirocaine who had relief was 49 minutes; for bupivacaine patients the median duration was 51 minutes. Following the first top-up injections, 91% of patients receiving Chirocaine and 90% of patients receiving bupivacaine achieved pain relief.

Epidural Administration for Surgery

Chirocaine concentrations of 0.50% and 0.75% administered by epidural injection were evaluated in 85 patients undergoing lower limb or major abdominal surgery in randomized, double-blind comparisons to bupivacaine. Anesthesia sufficient for surgery was achieved in almost all patients on either treatment. In patients having abdominal surgery, the mean (± s.d.) time to onset of sensory block was 14 ± 6 minutes for Chirocaine and 14 ±10 minutes for bupivacaine. With respect to the duration of block, the time to complete regression was 551 ± 88 minutes for Chirocaine and 506 ± 71 minutes for bupivacaine.

Post-Operative Pain Management

Post-operative pain control was evaluated in 258 patients in three studies including one dose-ranging study and two studies assessing Chirocaine in combination with epidural fentanyl or clonidine. The dose ranging study evaluated Chirocaine in concentrations of 0.0625%, 0.125%, and 0.25% Chirocaine in patients undergoing orthopedic surgery; the highest concentration was significantly more effective than were the other two concentrations. The Chirocaine combination studies in post-operative pain management tested 0.125% Chirocaine in combination with 4 µg/mL fentanyl and 0.125% Chirocaine in combination with clonidine 50 µg/hour in

orthopedic surgery. In these studies, the efficacy variable was time to first request for rescue analgesia during the 24 hour epidural infusion period. In both studies, the combination treatment provided better pain control than clonidine, opioid or local anesthetic alone.

Peripheral Nerve Administration

Chirocaine has been evaluated for its anesthetic efficacy when used as a peripheral nerve block. These clinical trials included brachial plexus (by supraclavicular approach) block study, infiltration anesthesia studies (for inguinal hernia repair), and peribulbar block studies.

Brachial Plexus Block

Chirocaine 0.25% and 0.50% were compared with 0.5% bupivacaine in 74 patients receiving a brachial plexus (supraclavicular) block for elective surgery. In the Chirocaine 0.25% treated group 68% of patients achieved satisfactory block and in the Chirocaine 0.5% treated group, 81% of patients achieved satisfactory block for surgery. In the bupivacaine 0.5% treated group, 74% of patients achieved satisfactory block for surgery.

Infiltration Anesthesia

Chirocaine 0.25% was evaluated in 68 patients in two randomized, double blind, bupivacaine controlled clinical trials for infiltration anesthesia during surgery and for post-operative pain management in patients undergoing inguinal hernia repair. No clear differences between the treatments were seen.

Peribulbar Block Anesthesia

Two clinical trials were conducted to evaluate 0.75% Chirocaine and bupivacaine in 110 patients for peribulbar block for anterior segment ophthalmic surgery, including cataract, glaucoma, and graft surgery, and for post-operative pain management. In one study, a 10 mL injection of 0.75% Chirocaine or bupivacaine produced a block adequate for surgery at a median time of 10 minutes. In the second study, a 5 mL dose of 0.75% Chirocaine or bupivacaine injected in a technique more closely resembling a retrobulbar block resulted in a median time to adequate block of 2 minutes for both treatments. Post-operative pain was reported in fewer than 10% of patients overall.

INDICATIONS AND USAGE

Chirocaine is indicated for the production of local or regional anesthesia for surgery and obstetrics, and for post-operative pain management.

Surgical Anesthesia: Epidural, peripheral neural blockade; and local infiltration.

Pain Management: continuous epidural infusion or intermittent epidural neural blockade; continuous or intermittent peripheral neural blockade or local infiltration.

For continuous epidural analgesia, Chirocaine may be administered in combination with epidural fentanyl or clonidine.

CONTRAINDICATIONS

Chirocaine is contraindicated in patients with a known hypersensitivity to Chirocaine or to any local anesthetic agent of the amide type.

WARNINGS

IN PERFORMING CHIROCAINE BLOCKS, UNINTENDED INTRAVENOUS INJECTION IS POSSIBLE AND MAY RESULT IN CARDIAC ARREST. DESPITE RAPID DETECTION AND APPROPRIATE TREATMENT, PROLONGED RESUSCITATION MAY BE REQUIRED. THE RESUSCITABILITY RELATIVE TO BUPIVACAINE IS UNKNOWN AT THIS POINT IN TIME AS IT HAS NOT BEEN STUDIED. AS WITH ALL LOCAL ANESTHETICS OF THE AMIDE TYPE, CHIROCAINE SHOULD BE ADMINISTERED IN INCREMENTAL DOSES. SINCE CHIROCAINE SHOULD NOT BE INJECTED RAPIDLY IN LARGE DOSES, IT IS NOT RECOMMENDED FOR EMERGENCY SITUATIONS, WHERE A FAST ONSET OF SURGICAL ANESTHESIA IS NECESSARY.

HISTORICALLY, PREGNANT PATIENTS WERE REPORTED TO HAVE A HIGH RISK FOR CARDIAC ARRHYTHMIAS, CARDIAC/CIRCULATORY ARREST AND DEATH WHEN BUPIVACAINE WAS INADVERTENTLY RAPIDLY INJECTED INTRAVENOUSLY. AVOID 0.75% CHIROCAINE IN OBSTETRICAL PATIENTS. THIS CONCENTRATION IS INDICATED ONLY FOR NON-OBSTETRICAL SURGERY REQUIRING PROFOUND MUSCLE RELAXATION AND LONG DURATION.

FOR CESARIAN SECTION, THE 5 MG/ML (0.5%) CHIROCAINE SOLUTION IN DOSES UP TO 150 MG IS RECOMMENDED.

LOCAL ANESTHETICS SHOULD ONLY BE ADMINISTERED BY CLINICIANS WHO ARE WELL VERSED IN THE DIAGNOSIS AND MANAGEMENT OF DRUG-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK BEING ADMINISTERED. THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES MUST BE ENSURED. (see also **ADVERSE REACTIONS** and **PRECAUTIONS**). DELAY IN PROPER MANAGEMENT OF DRUG-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE, AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST, AND POSSIBLY DEATH.

SOLUTIONS OF CHIROCAINE SHOULD NOT BE USED FOR THE PRODUCTION OF OBSTETRICAL PARACERVICAL BLOCK ANESTHESIA. THERE ARE NO DATA TO SUPPORT SUCH USE AND THERE IS THE ADDITIONAL RISK OF FETAL BRADYCARDIA AND DEATH.

INTRAVENOUS REGIONAL ANESTHESIA (BIER BLOCK) SHOULD NOT BE PERFORMED USING CHIROCAINE BECAUSE OF THE LACK OF CLINICAL EXPERIENCE AND THE RISK OF ATTAINING TOXIC BLOOD LEVELS OF LEVOBUPIVACAINE.

It is essential that aspiration for blood or cerebrospinal fluid (where applicable), be done prior to injecting any local anesthetic, both before the original dose and all subsequent doses, to avoid intravascular or intrathecal injection. However, a negative aspiration does *not* ensure against intravascular or intrathecal injection. Chirocaine should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive.

When contemplating a peripheral nerve block, where large volumes of local anesthetic are needed, caution should be exercised when using the higher mg/mL concentrations of Chirocaine. Animal studies demonstrate CNS and cardiac toxicity that is dose related, thus equal volumes of higher concentration will be more likely to produce cardiac toxicity.

PRECAUTIONS

General:

The safe and effective use of local anesthetics depends on proper dosage, correct technique, adequate precautions, and readiness for emergencies.

Resuscitative equipment, oxygen, and resuscitative drugs should be available for immediate use (see **WARNINGS** and **ADVERSE REACTIONS**). The lowest dosage that results in effective anesthesia should be used to avoid high plasma or dermatomal levels and serious adverse effects. Injections should be made slowly and incrementally, with frequent aspirations before and during the injection to avoid intravascular injection. When a continuous catheter technique is used, syringe aspirations should also be performed before and during each supplemental injection. During the administration of epidural anesthesia, it is recommended that a test dose of a local anesthetic with a fast onset be administered initially and that the patient be monitored for central nervous system and cardiovascular toxicity, as well as for signs of unintended intrathecal administration before proceeding. When clinical conditions permit, consideration should be given to employing local anesthetic solutions that contain epinephrine for the test dose because circulatory changes compatible with epinephrine may also serve as a warning sign of unintended intravascular injection. An intravascular injection is still possible even if aspirations for blood are negative.

Injection of repeated doses of local anesthetics may cause significant increases in plasma levels with each repeated dose due to slow accumulation of the drug or its metabolites or to slow metabolic degradation. Tolerance to elevated blood levels varies with the physical condition of the patient. Local anesthetics should also be used with caution in patients with hypotension, hypovolemia, or impaired cardiovascular function, especially heart block.

Careful and constant monitoring of cardiovascular and respiratory vital signs (adequacy of ventilation) and the patient's state of consciousness should be performed after each local anesthetic injection. The clinician must be aware that restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.

Amide-type local anesthetics such as Chirocaine are metabolized by the liver, therefore these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk for developing toxic plasma concentrations. Local anesthetics should also be used with caution in patients with impaired cardiovascular function as they may be less able to compensate for functional changes associated with prolonged A-V conduction caused by these drugs.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for malignant hyperthermia. Amide-type local anesthetics are not known to trigger this reaction.

Epidural Anesthesia

During epidural administration, Chirocaine should be administered in incremental volumes of 3 to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Syringe aspirations should also be performed before and during each supplemental injection in continuous catheter techniques. An intravascular injection is still possible even if aspirations for blood are negative. During the administration of epidural anesthesia, it is recommended that a test dose is administered initially and the effects monitored before the full dose is given. A test dose of a short-acting amide anesthetic, such as 3 mL of lidocaine, is recommended to detect unintentional intrathecal administration. This will be manifested within a few minutes by signs of a subarachnoid block (e.g., decreased sensation of the buttocks, paresis of the legs or, in the sedated patient, absent knee jerk). Unintentional intrathecal injection of local anesthetics can lead to very high spinal anesthesia, possibly apnea, severe hypotension and loss of consciousness. An intravascular or intrathecal injection is still possible even if the results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, extensive subarachnoid block, or cardiovascular effects.

Use in Head and Neck Area:

Small doses of local anesthetics injected into the head and neck area may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care. Confusion, convulsions, respiratory depression, and/or respiratory arrest and cardiovascular stimulation or depression have been reported. These reactions may be due to intraarterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their respirations and circulation monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded (see DOSAGE AND ADMINISTRATION).

Information for Patients

When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity in the anesthetized part of the body following correct administration of regional anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the Chirocaine package insert.

Clinically Significant Drug-Drug Interactions

Chirocaine should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics since the toxic effects of these drugs could be additive. In vitro studies indicate CYP3A4 isoform and CYP1A2 isoform mediate the metabolism of levobupivacaine to desbutyl levobupivacaine and 3-hydroxy levobupivacaine, respectively. Thus agents likely to be concomitantly administered with Chirocaine that are metabolized by this isoenzyme family may potentially interact with Chirocaine. Although no clinical studies have been conducted, it is likely that the metabolism of levobupivacaine may be affected by the known CYP3A4 inducers (such as phenytoin, phenobarbital, rifampin), CYP3A4 inhibitors (azole antimycotics e.g. ketoconazole; certain protease inhibitors e.g. ritanovir; macrolide antibiotics e.g. erythromycin; and calcium channel antagonists e.g. verapamil), CYP1A2 inducers (omeprazole) and CYP1A2 inhibitors (furafylline and clarithromycin). Dosage adjustment may be warranted when levobupivacaine is concurrently administered with CYP3A4 inhibitors and CYP1A2 inhibitors as systemic levobupivacaine levels may rise resulting in toxicity.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals of most local anesthetics, including Chirocaine, to evaluate the carcinogenic potential have not been conducted. Mutagenicity was not observed in bacterial mutation assay, mouse lymphoma cells mutation assay, chromosome aberrations in human blood lymphocytes, and micronuclei in the bone marrow of treated mice. Studies performed with Chirocaine in rats at 30 mg/kg/day (180 mg/m^2/day) did not demonstrate an effect on fertility or general reproductive performance over two generations. This dose is approximately one-half the maximum recommended human dose (570 mg/person) based on body surface area (352 mg/m^2).

Pregnancy Category B

Teratogenicity studies in rats (180 mg/m^2/day) and rabbits (220 mg/m^2/day) did not show evidence of any adverse effects on organogenesis or early fetal development. The doses used were approximately one-half the maximum recommended human dose (570 mg/person or 352 mg/m^2) based on body surface area. There were no treatment-related effects on late fetal development,

parturition, lactation, neonatal viability, or growth of the offspring in a perinatal and postnatal study in rats at dose levels up to approximately one-half the maximum recommended human dose based on body surface area. There were no adequate and well-controlled studies in pregnant women of the effects of Chirocaine on the developing fetus. Chirocaine should only be used during pregnancy if the benefits outweigh the risks.

Labor and Delivery

Local anesthetics, including Chirocaine, rapidly cross the placenta, and, when used for epidural block, can cause varying degrees of maternal, fetal, and neonatal toxicity. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the central nervous system, peripheral vascular tone, and cardiac function. Maternal hypotension, fetal bradycardia and fetal decelerations have resulted from regional anesthesia with Chirocaine for obstetrical pain relief. Local anesthetics produce vasodilation by blocking sympathetic nerves. Administration of intravenous fluids, elevation of the patient's legs and left uterine displacement will help prevent decreases in blood pressure. The fetal heart rate should also be monitored continuously and electronic fetal monitoring is highly advisable.

Nursing Mothers

Some local anesthetic drugs are excreted in human milk and caution should be exercised when Chirocaine is administered to a nursing woman. The excretion of Chirocaine or its metabolites in human milk has not been studied. Studies in rats demonstrated that small amounts of Chirocaine can be detected in the pups after administration of Chirocaine to the nursing mothers (see **PRECAUTIONS**).

Pediatric Use

The safety and effectiveness of Chirocaine in pediatric patients have not been established.

Geriatric Use

Of the total number of subjects in clinical studies of Chirocaine, 16% were 65 and over, while 8% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Reactions to Chirocaine are characteristic of those associated with other amide-type local anesthetics. A major cause of the adverse reactions to this group of drugs is associated with excessive plasma levels, or high dermatomal levels, which may be due to overdose, unintentional intravascular injection, or slow metabolic degradation. The reported adverse events are derived from studies conducted in the United States and Europe. The reference drug was primarily bupivacaine. While the adverse event profile from clinical trials in patients was similar between the two drugs, their relative potency has not been established The studies were conducted using a variety of premedications, sedatives, and surgical procedures of varying length. A total of 1220 were exposed to Chirocaine. Each patient was counted once for each type of adverse event.

In the Phase II/III studies, 78% of patients who received Chirocaine reported at least one adverse event. Of those patients who received the 0.75% levobupivacaine concentration, 85% reported at least one adverse event.

Adverse events that occurred in >5% of all Chirocaine-treated patients in Phase II / III studies (N=1141) were hypotension (31%), nausea (21%), post-operative pain (18%), fever (17%), vomiting (14%), anemia (12%), pruritus (9%), pain (8%), headache (7%), constipation (7%), dizziness (6%), and fetal distress (5%).

ADVERSE EVENTS REPORTED WITH AN INCIDENCE OF ≥1% IN THE PHASE II/III BUPIVACAINE-CONTROLLED STUDIES

Event	Levobupivacaine N=509		Bupivacaine N=453	
	n	(%)	n	(%)
Hypotension	100	(19.6)	93	(20.5)
Nausea	59	(11.6)	66	(14.6)
Anemia	49	(9.6)	37	(8.2)
Post-operative Pain	37	(7.3)	37	(8.2)
Vomiting	42	(8.3)	30	(6.6)
Back Pain	29	(5.7)	19	(4.2)
Fever	33	(6.5)	35	(7.7)
Dizziness	26	(5.1)	22	(4.9)
Fetal Distress	49	(9.6)	41	(9.1)
Headache	23	(4.5)	18	(4.0)
Delivery Delayed	32	(6.3)	31	(6.8)
Pruritus	19	(3.7)	26	(5.7)
Pain	18	(3.5)	17	(3.8)
ECG Abnormal	16	(3.1)	17	(3.8)
Abdomen Enlarged	15	(2.9)	12	(2.6)
Albuminuria	15	(2.9)	6	(1.3)
Rigors	15	(2.9)	12	(2.6)
Constipation	14	(2.8)	20	(4.4)
Diplopia	13	(2.6)	14	(3.1)
Hypoesthesia	13	(2.6)	15	(3.3)
Flatulence	12	(2.4)	11	(2.4)
Abdominal Pain	11	(2.2)	6	(1.3)
Hypothermia	11	(2.2)	6	(1.3)
Bradycardia	11	(2.2)	10	(2.2)
Dyspepsia	10	(2.0)	11	(2.4)

Hematuria	10	(2.0)	5	(1.1)
Hemorrhage in Pregnancy	9	(1.8)	12	(2.6)
Paresthesia	9	(1.8)	2	(0.4)
Tachycardia	9	(1.8)	7	(1.5)
Urine Abnormal	9	(1.8)	6	(1.3)
Purpura	7	(1.4)	4	(0.9)
Wound Drainage Increased	7	(1.4)	13	(2.9)
Coughing	6	(1.2)	3	(0.7)
Leukocytosis	6	(1.2)	3	(0.7)
Somnolence	6	(1.2)	4	(0.9)
Urinary Incontinence	6	(1.2)	1	(0.2)
Anesthesia Local	5	(1.0)	5	(1.1)
Anxiety	5	(1.0)	6	(1.3)
Breast Pain (Female)	5	(1.0)	4	(0.9)
Hypertension	5	(1.0)	8	(1.8)
Urine Flow Decreased	5	(1.0)	3	(0.7)
Urinary Tract Infection	5	(1.0)	3	(0.7)
Diarrhea	5	(1.0)	6	(1.3)

The following adverse events were reported during the Chirocaine clinical program in more than one patient and occurred at an overall incidence of <1%, and were considered clinically relevant;

Body as a Whole: asthenia, edema.

Cardiovascular Disorders, General, postural hypotension.

Central and Peripheral Nervous System Disorders: hypokinesia, involuntary muscle contraction, spasm (generalized), tremor, syncope.

Heart Rate and Rhythm Disorders: arrhythmia, extrasystoles, fibrillation (atrial),.and cardiac arrest.

Gastrointestinal System Disorders: ileus.

Liver and Biliary System Disorders: elevated bilirubin.

Psychiatric Disorders: confusion.

Respiratory System Disorders: apnea, bronchospasm, dyspnea, pulmonary edema, respiratory insufficiency.

Skin and Appendage Disorders: increased sweating, skin discoloration.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels or high dermatomal levels ("high spinal") encountered during therapeutic use of local anesthetics or to unintended intrathecal or intravascular injection of local anesthetic solution (see **ADVERSE REACTIONS, WARNINGS,** and **PRECAUTIONS**). There was one case of suspected unintentional intravascular injection which occurred during the clinical trial program. That patient received 19 mL of 0.75% levobupivacaine (142.5 mg) and experienced CNS excitation which was treated with thiopental. No abnormal cardiovascular changes were observed and the patient recovered without sequelae.

Management of Local Anesthetic Emergencies

The first consideration is prevention, best accomplished by incremental injection of Chirocaine, careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection and during continuous infusion. At the first sign of change, oxygen should be administered.

The first step in the management of systemic toxic reactions, as well as underventilation or apnea due to unintentional subarachnoid injection of drug solution, consists of immediate attention to the establishment and maintenance of a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask. This may prevent convulsions if they have not already occurred.

If necessary, use drugs to control convulsions. Intravenous barbiturates, anti-convulsant agents, or muscle relaxants should only be administered by those familiar with their use. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated. Supportive treatment of circulatory depression may require administration of intravenous fluids, and, when appropriate, a vasopressor dictated by the clinical situation (such as ephedrine or epinephrine to enhance myocardial contractile force).

If difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated, endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated after initial administration of oxygen by mask.

The supine position is dangerous in pregnant women at term because of aortacaval compression by the gravid uterus. Therefore, during treatment of systemic toxicity, maternal hypotension or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels should be accomplished. Resuscitation of obstetrical patients may take longer than resuscitation of non-pregnant patients and closed-chest cardiac compression may be ineffective. Rapid delivery of the fetus may improve the response to resuscitation efforts.

DOSAGE AND ADMINISTRATION

The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should always be used. The smallest dose and concentration required to produce the desired result should be administered. The dose of any local anesthetic differs with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the intensity of the block, the degree of muscle relaxation required, the duration of the anesthesia desired, individual tolerance, and the physical condition of the patient. Patients in poor general condition due to aging or other compromising factors such as impaired cardiovascular function, advanced liver disease, or severe renal dysfunction, require special attention.

To reduce the risk of potentially serious adverse reactions, attempts should be made to optimize the patient's condition before major blocks are performed, and the dosage should be adjusted accordingly. Use an adequate test dose (3-5 mL) of a short-acting local anesthetic solution containing epinephrine prior to induction of complete nerve block. This test dose should be repeated if the patient is moved in such a fashion as to have displaced the epidural catheter. It is recommended that adequate time be allowed for the onset of anesthesia following administration of each test dose.

Disinfecting agents containing heavy metals, which cause release of ions (mercury, zinc, copper, etc.), should not be used for skin or mucous membrane disinfection since they have been related to incidents of swelling and edema.

When chemical disinfection of the container surface is desired, either isopropyl alcohol (91%) or ethyl alcohol (70%) is recommended. It is recommended that chemical disinfection be accomplished by wiping the vial stopper thoroughly with cotton or gauze that has been moistened with the recommended alcohol just prior to use.

When a container is required to have a sterile outside, glass containers may be autoclaved once. Stability has been demonstrated following an autoclave cycle at 121°C for 15 minutes.

These products are intended for single use and do not contain preservatives; any solution remaining from an open container should be discarded.

For specific techniques and procedures, refer to standard contemporary textbooks.

Chirocaine Compatibility and Admixtures

Chirocaine may not be compatible with alkaline solutions having a pH greater than 8.5. Studies have shown that Chirocaine is compatible with 0.9% Sodium Chloride Injection USP and with saline solutions containing morphine, fentanyl, and clonidine. Compatibility studies with other parenteral products have not been studied.

Dilution Stability

Chirocaine diluted to 0.625 - 2.5 mg levobupivacaine per mL in 0.9% Sodium Chloride Injection is physically and chemically stable when stored in PVC (polyvinyl chloride) bags at ambient room temperature for up to 24 hours. Aseptic techniques should be used to prepare the diluted product. Admixtures of Chirocaine should be prepared for single patient use only and used within 24 hours of preparation. The unused portion of diluted Chirocaine should be discarded after each use.

NOTE: Parenteral products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions that are not clear and colorless should not be used.

Dosage Recommendations:

	Concentration %	Dose mL	Dose mg	Motor Block
Surgical Anesthesia				
Epidural for surgery	0.5-0.75	10-20	50-150	Moderate to complete
Epidural for Cesarean Section	0.5	20-30	100-150	Moderate to complete
Peripheral Nerve	0.25-0.5	30 0.4 mL/kg	75-150 1-2 mg/kg	Moderate to complete
Ophthalmic	0.75	5-15	37.5-112.5	Moderate to complete
Local Infiltration	0.25	60	150	Not Applicable
Pain Management [a]				
Labor Analgesia (epidural bolus)	0.25	10-20	25-50	Minimal to moderate
Post-operative pain (epidural infusion)	0.125-0.25[b]	4-10 mL/h	5-25 mg/h	Minimal to moderate

[a] In pain management Chirocaine can be used epidurally with fentanyl or clonidine.

[b] Dilutions of Chirocaine standard solutions should be made with preservative free 0.9% saline according to standard hospital procedures for sterility.

The doses in the table are those considered to be necessary to produce a successful block and should be regarded as guidelines for use in adults. Individual variations in onset and duration occur.

Epidural doses of up to 375 mg have been administered incrementally to patients during a surgical procedure.

The maximum dose in 24 hours for intraoperative block and postoperative pain management was 695 mg.

The maximum dose administered as a post-operative epidural infusion over 24 hours was 570 mg.

The maximum dose administered to patients as a single fractionated injection was 300 mg for brachial plexus block.

HOW SUPPLIED

Chirocaine, 2.5 mg levobupivacaine in each mL.

10 mL Single Use Vials. (NDC 59011-997-10)

30 mL Single Use Vials. (NDC 59011-997-30)

Chirocaine, 5.0 mg levobupivacaine in each mL.

10 mL Single Use Vials. (NDC 59011-998-10)

30 mL Single Use Vials. (NDC 59011-998-30)

Chirocaine, 7.5 mg levobupivacaine in each mL.

10 mL Single Use Vials. (NDC 59011-999-10)

30 mL Single Use Vials. (NDC 59011-999-30)

STORAGE

Store Chirocaine at controlled room temperature, 20 - 25°C (68 - 77°F), excursions permitted to 15 - 30°C (59 - 86°F).

Rx ONLY.

Manufactured by

Ben Venue Laboratories, Inc.
Bedford, OH 44146

Distributed by

Purdue Pharma L.P.
Norwalk, CT 06850-3590

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