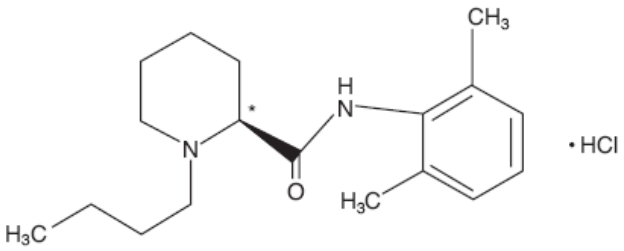
Chirocaine®
Levobupivacaine HCl

DESCRIPTION
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 C18H28N2O•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).

Levobupivacaine 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. Levobupivacaine is preservative free and is available in 10 mL single dose ampules.

CLINICAL PHARMACOLOGY
Levobupivacaine 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.

Pharmacodynamics
Levobupivacaine can be expected to share the pharmacodynamic properties of other local anesthetics. Systemic absorption of local anesthetics can produce effects on the central nervous system 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 levobupivacaine and bupivacaine in animal species, both the central nervous system (CNS) and the cardiac toxicity of levobupivacaine were less than that of bupivacaine. Arrhythmogenic effects were seen in animal at higher doses of levobupivacaine than bupivacaine. 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 mcg/mL and 1.6 mcg/mL. In a second study following a three-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 levobupivacaine and bupivacaine on the electroencephalogram (EEG) following an intravenous dose (40 mg) that was predicted to be below the threshold to cause central nervous system (CNS) symptoms. In this study, levobupivacaine decreased high alpha power in 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 levobupivacaine 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 levobupivacaine and 48 mg (range 22.5 - 110 mg) for bupivacaine. The primary endpoints of the study were cardiac contractility and standard electrocardiographic parameters. Both drugs produced transient increases in heart rate and systolic and diastolic pressure, but the change in diastolic pressure was significantly less with levobupivacaine than with bupivacaine. Cardiac function measured by transthoracic electrical bioimpedeance showed significant differences in that levobupivacaine produced a lesser reduction in stroke index, the acceleration index, and the ejection fraction.

A double-blind, randomized, parallel group trial was conducted on 22 healthy male volunteers to compare the effects of levobupivacaine and bupivacaine on QT dispersion and signal averaged ECG. The objective of the trial was to determine the effect of levobupivacaine and bupivacaine on myocardial depolarization and repolarization as measured by the QRS duration of signal-averaged ECGs, QT dispersion, and other ECG variables. During double-blind dosing, subjects received either levobupivacaine or bupivacaine in tolerated doses ranging from 30 mg to 120 mg. The results showed that ten of eleven bupivacaine subjects experienced CNS systems compared with six of eleven levobupivacaine subjects. In those subjects who received more than 75 mg of randomized drug, the maximum changes from baseline QTc interval was statistically significantly lower for levobupivacaine (3 ± 11 msec) than bupivacaine (24 ± 17 msec, p=0.022). No other statistically significant changes were seen in cardiac parameters.

CLINICAL TRIALS

The clinical trial program included 1220 patients and subjects who received levobupivacaine in 31 clinical trials. Levobupivacaine 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 postoperative pain control. Clinical trials have demonstrated that levobupivacaine and bupivacaine exhibit similar anesthetic effects (see **CLINICAL PHARMACOLOGY**).

Central Administration

Epidural Administration in Cesarean Section

In one study, levobupivacaine 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 (±SD) time to sensory block measured at T4 to T6 was 10 ± 8 minutes for levobupivacaine and 6 ± 4 minutes for bupivacaine. The mean duration of sensory block and motor block was 8 ± 1 and 4 ± 1 hours for levobupivacaine and 7 ± 1 and 4 ± 1 hours for bupivacaine, respectively. Ninety-four percent of patients receiving levobupivacaine 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 levobupivacaine and bupivacaine was 10 ± 7 minutes and 9 ± 7 minutes, respectively, with 94% of levobupivacaine 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
Levobupivacaine 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% levobupivacaine 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 levobupivacaine and 90% of patients receiving bupivacaine achieved pain relief.

Epidural Administration for Surgery
Levobupivacaine 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 (±SD) time to onset of sensory block was 14 ± 6 minutes for levobupivacaine and 14 ± 10 minutes for bupivacaine. With respect to the duration of block, the time to complete regression was 551 ± 88 minutes for levobupivacaine and 506 ± 71 minutes for bupivacaine.

Post-Operative Pain Management
Post-operative pain control was evaluated in 324 patients in four studies including one dose-ranging study and three studies assessing levobupivacaine in combination with epidural fentanyl, morphine or clonidine. The dose-ranging study evaluated levobupivacaine in concentrations of 0.0625%, 0.125%, and 0.25% in patients undergoing orthopedic surgery; the highest concentration was significantly more effective than were the other two concentrations. The levobupivacaine combination studies in postoperative pain management tested 0.125% levobupivacaine in combination with 4 mcg/mL fentanyl, 0.125% levobupivacaine in combination with clonidine 50 mcg/hour in orthopedic surgery, and 0.25% levobupivacaine and 0.005% morphine in abdominal surgery. In these studies, the efficacy variable was time to first request for rescue analgesia during the 24-hour epidural infusion period. In the studies, the combination treatment provided better pain control than clonidine, opioid or local anesthetic alone.

There is limited safety experience with levobupivacaine therapy for period exceeding 24 hours. Therefore, use of levobupivacaine is not recommended for more than 24 hours.

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

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

Levobupivacaine 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 treatments were seen.

Peribulbar Block Anesthesia
Two clinical trials were conducted to evaluate 0.75% levobupivacaine 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 ten mL (10 mL) injection of 0.75% levobupivacaine or bupivacaine produced a block adequate for surgery at a median time of ten minutes. In the second study, a five mL (5 mL) dose of 0.75% levobupivacaine or bupivacaine injected in a technique more closely resembling a retrobulbar block resulted in a median time to adequate block of two minutes for both treatments. Post-operative pain was reported in fewer than ten percent of patients overall.

Pharmacokinetics

Table 1. Pharmacokinetic parameter values of levobupivacaine after 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} , mcg/mL	1.445 ± 0.237	1.421 ± 0.224	0.629 ± 0.100	0.794 ± 0.131
$AUC_{0-\infty}$, mcg hour/mL	1.153 ± 0.447	1.166 ± 0.400	0.478 ± 0.166	0.715 ± 0.261
$t_{1/2}$, 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

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

A comparison of the estimates for plasma AUC and Cmax between levobupivacaine and bupivacaine in two Phase III clinical trial involving short duration administration of either agent found that neither total plasma exposure or Cmax differed between the two drugs when compared within studies. Between study values differed somewhat, likely due to differences in injection sites, volume, and total dose administered in each of the studies. These data suggest that levobupivacaine and bupivacaine have a similar pharmacokinetic profile. Pharmacokinetic data from the two Phase III studies are presented in Table 2.

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**		
	Levobupivacaine		**Bupivacaine**	**Levobupivacaine**		**Bupivacaine**
Conc. (%)	0.50	0.75	0.50	0.25	0.50	0.50
Dose Received	75 mg	112.5 mg	75 mg	1 mg/kg	2 mg/kg	2 mg/kg
n	9	9	8	10	10	9
Cmax (mcg/mL)	0.582	0.811	0.414	0.474	0.961	1.029
Tmax (hour)	0.52	0.44	0.36	0.50	0.71	0.68
AUC(0 - t) (mcg.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.

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 mcg/mL.

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

Levobupivacaine is extensively metabolized with no unchanged levobupivacaine detected in urine and 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 in both in vitro and in vivo.

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.

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 **WARNINGS AND 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.

INDICATIONS

Adults

Levobupivacaine is indicated in adults for:

Surgical Anesthesia
Major: Epidural (including for cesarean section), intrathecal, peripheral nerve block.
Minor: Local infiltration, peribulbar block in ophthalmic surgery

For cesarean section, the 7.5 mg/mL concentration is not recommended (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS**).

Pain Management
Continuous epidural infusion, single or multiple bolus administration for post-operative, labor or chronic pain.

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

For labor analgesia, the 7.5 mg/mL concentration is not recommended (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, PREGNANCY AND LACTATION – Labor and Delivery)

Children

Levobupivacaine is indicated in children for infiltration analgesia (ilioinguinal/iliohypogastric blocks) (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

General contraindications related to regional anesthesia should be taken into account with the use of any regional anesthetic agent, including levobupivacaine. Levobupivacaine solutions are contraindicated in those with a known sensitivity to local anesthetic amide agents.

Levobupivacaine is contraindicated in patients with severe hypotension such as cardiogenic or hypovolemic shock (see **WARNINGS AND PRECAUTIONS**).

Levobupivacaine solutions 2.5 mg/mL, 5 mg/mL, and 7.5 mg/mL, are contraindicated for use in paracervical block in obstetrics, and for intravenous regional anesthesia (e.g. Bier block).

Additionally, levobupivacaine 7.5 mg/mL solution should not be employed for any obstetric procedures. Contraindications for use in paracervical block, Bier block, and levobupivacaine 7.5 mg/mL use in obstetric procedures are based upon documented experiences with bupivacaine. Levobupivacaine has not been tested in such instances.

WARNINGS AND PRECAUTIONS

In performing levobupivacaine blocks, unintended intravenous injection is possible and may result in cardiac arrest (some cases fatal). 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, levobupivacaine should be administered in incremental doses. Cases of severe bradycardia, hypotension and respiratory compromise with cardiac arrest (some of them fatal), have been reported in conjunction with local anesthetics, including levobupivacaine. Since levobupivacaine 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.

For cesarean section, the 5 mg/mL (0.5%) levobupivacaine 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**). 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.

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 levobupivacaine. 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.

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 **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.

Systemic adverse reactions following overdose or accidental intravascular injection reported with long local anesthetic agents involve both CNS and cardiovascular effects.

Levobupivacaine should be used with caution in conditions associated with impaired cardiovascular function (see **CONTRAINDICATIONS**).

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 signs of central nervous system toxicity.

Amide-type local anesthetics, such as levobupivacaine, 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 anesthesia, levobupivacaine should be administered in incremental volumes of three to five milliliters (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 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 three milliliters (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.

Epidural Analgesia
There are limited clinical trial data with levobupivacaine therapy for periods exceeding 24 hours. There have been postmarketing reports of cauda equina syndrome and events indicative of neurotoxicity (see **ADVERSE REACTIONS**) temporally associated with the use of levobupivacaine for greater than or equal to 24 hours for epidural analgesia. These events were more severe and in some cases led to permanent sequelae when levobupivacaine was administered for greater than 24 hours. Therefore, the use of levobupivacaine is not recommended for more than 24 hours.

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. Levobupivacaine 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.

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 the Patient
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 the regional anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the levobupivacaine package insert.

DRUG INTERACTIONS
Levobupivacaine 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 levobupivacaine that are metabolized by this isoenzyme

family may potentially interact with levobupivacaine. 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 antimyotics, e.g. ketoconazole; certain protease inhibitors, e.g. ritonavir; macrolide antibiotics, e.g. erythromycin; and calcium channel antagonists, e.g. verapamil), CYP1A2 inducers (omeprazole) and CYP1A2 inhibitors (furafylline and clarithromycin). Dosage adjustments may be warranted when levobupivacaine is concurrently administered with CYP3A4 inhibitors and CYP1A2 inhibitors, as systemic levobupivacaine levels may rise resulting in toxicity.

Levobupivacaine should be used with caution in patients receiving anti-arrhythmic agents with local anesthetic activity, e.g. mexilitine, or class III ant-arrhythmic agents since their use may be additive.

PREGNANCY AND LACTATION

Pregnancy

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 levobupivacaine on the developing fetus. Levobupivacaine should only be used during pregnancy if the benefits outweigh the risks.

Labor and Delivery

Local anesthetics, including levobupivacaine, 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 levobupivacaine 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.

The 7.5 mg/mL solution is not recommended for obstetric use due to an enhanced risk for cardiotoxic events based on experience with bupivacaine. There is no experience of levobupivacaine 7.5 mg/mL in obstetric surgery.

Nursing Mothers

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

Geriatrics

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

ADVERSE REACTIONS

Reactions to levobupivacaine are characteristic of those associated with other amide-type 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. The studies were conducted using a variety of premedications, sedatives, and surgical procedures of varying lengths. A total of 1220 were exposed to levobupivacaine. Each patient was counted once for each type of adverse event.

In Phase II/III studies, 78% of patients who received levobupivacaine 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 Levobupivacaine-Treated Patients In Phase II/III Studies (N=1141)

Hypotension (31%)	Pruritis (9%)
Nausea (21%)	Pain (8%)
Post-operative pain (18%)	Headache (7%)
Fever (17%)	Constipation (7%)
Vomiting (14%)	Dizziness (6%)
Anemia (12%)	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	
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)
Delayed Delivery	32	(6.3)	31	(6.8)
Pruritis	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)
Albuminemia	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 levobupivacaine 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), 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

Reactions to levobupivacaine are characteristic of those associated with other amide-type local anesthetics. Systems involved may include the central nervous system, the cardiovascular system, and the respiratory system (see **WARNINGS AND PRECAUTIONS** and **OVERDOSAGE**).

The incidences of adverse neurological reactions associated with the use of local anesthetics may be related to the total dose of anesthetic administered and are also dependent upon the particular drug used, the route of administration, and the physical status of the patient. Many of these effects may be related to local anesthetic techniques, with or without contribution from the drug.

Allergic-type reactions are rare and may occur as a result of sensitivity to the local anesthetic. These reactions are characterized by signs such as urticaria, pruritis, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and, possibly, anaphylactoid-like symptomatology (including severe hypotension). Cross sensitivity among members of the amide-type local anesthetic group have been reported.

Postmarketing reports
Anaphylaxis has been reported. Very rare reports of convulsions have occurred following accidental intravenous administration.

There have been reports of prolonged weakness or sensory disturbance, some of which may have been permanent, in association with levobupivacaine therapy. It is difficult to determine whether the long-term effects were the result of medication toxicity or unrecognized trauma during surgery or other mechanical factors, such as catheter insertion and manipulation.

Reports have been received of cauda equine syndrome or signs and symptoms of potential injury to the base of the spinal cord or spinal nerve roots (including lower extremity paresthesias, weakness or paralysis, loss of bowel control and/or bladder control and priapism) associated with levobupivacaine

administration. These events were more severe and in some cases did not resolve when levobupivacaine was administered for greater than 24 hours (see **WARNINGS AND PRECAUTIONS**). However, it cannot be determined whether these events are due to an effect of levobupivacaine, mechanical trauma to the spinal cord or spinal nerve roots, or blood collection at the base of the spine.

There have also been reports of transient Horner's syndrome (ptosis, miosis, enophthalmus, unilateral sweating and/or flushing) in association with use of regional anesthetics, including levobupivacaine. This event resolves with discontinuation of therapy.

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** and **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 cardiac 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 levobupivacaine, 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, and further measures as warranted.

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 to 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.

The use of levobupivacaine is not recommended for more than 24 hours (see **WARNINGS AND PRECAUTIONS**).

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 ampule thoroughly with cotton or gauze that has been moistened with the recommended alcohol prior to use.

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.

Levobupivacaine Compatibility and Admixtures
Levobupivacaine may not be compatible with alkaline solutions having a pH greater than 8.5. Studies have shown that levobupivacaine 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
Levobupivacaine 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 technique should be used to prepare the diluted products. Admixtures of levobupivacaine should be prepared for single patient use only and used within 24 hours of preparation. The unused portion of diluted levobupivacaine 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.

Shelf Life
Shelf life after first opening: The product should be used immediately.

Shelf life after dilution: Chemical and physical in-use stability has been demonstrated for seven days at 20 - 22°C. Chemical and physical in-use stability with clonidine, morphine or fentanyl has been demonstrated for 40 hours at 20 - 22°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

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	15 - 30	75 - 150	Moderate to Complete
Peripheral Nerve	0.25 - 0.5	1 - 40	maximum 150	Moderate to Complete
Intrathecal	0.5	3	15	Moderate to Complete
Ophthalmic	0.75	5 - 15	37.5 - 112.5	Moderate to Complete
Local Infiltration - Adults	0.25	1-60	maximum 150	Not applicable
Local Infiltration - Children < 12 yrs[d]	0.25	0.50 mL/kg/side	1.25 mg/kg/side	Not applicable
	0.5	0.25 mL/kg/side	1.25 mg/kg/side	Not applicable
Pain Management[a b]				
Labor Analgesia (epidural bolus)	0.25	10 - 20	25 - 50	Minimal to Moderate
Labor Analgesia (epidural infusion)	0.125[c]	4 - 10 mL/h	5 - 12.5 mg/h	Minimal to Moderate
Post-Operative Pain (epidural infusion)	0.125[c]	10-15 mL/h	12.5 - 18.75 mg/h	Minimal to Moderate
	0.25[c]	5 – 7.5 mL/h	12.5 - 18.75 mg/h	Minimal to Moderate

[a] In pain management levobupivacaine can be used epidurally with fentanyl, morphine or clonidine.
[b] In cases where levobupivacaine is combined with other agents e.g. opioids in pain management, the levobupivacaine dose should be reduced as use of a lower concentration (e.g. 1.25 mg/mL) is preferable.

[c] Dilutions of levobupivacaine standard solutions should be made with preservative free 0.9% saline according to standard hospital procedures for sterility.
[d] No data are available in pediatric population < 6 months of age.
The doses in the table are those considered to be necessary to produce a successful block and should be regarded as guidelines for use. 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 post-operative 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.

For cesarean section, the maximum recommended dose is 150 mg.

In children, the maximum recommended dose for infiltration analgesia (ilioinguinal-iliohypogastric block) is 1.25 mg/kg/side.

PRE-CLINICAL SAFETY DATA

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals of most local anesthetics, including levobupivacaine, 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 levobupivacaine 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).

STORAGE
Store levobupivacaine at 15 - 30°C (59 - 86°F).

HOW SUPPLIED
Chirocaine, 2.5 mg levobupivacaine in each mL.

List No.	**Size**
P222	10 mL Single Use Plastic Ampules

Chirocaine, 5.0 mg levobupivacaine in each mL.

List No.	**Size**
P223	10 mL Single Use Plastic Ampules

Chirocaine, 7.5 mg levobupivacaine in each mL.

List No.	**Size**
P224	10 mL Single Use Plastic Ampules

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