SPECTRA MEDICAL DEVICES, INC.

SODIUM CHLORIDE INJECTION, USP, 0.9%

DESCRIPTION
Sodium Chloride Injection, USP is a sterile, nonpyrogenic, isotonic solution of sodium chloride 0.9% (9mg/mL) in Water for Injection containing no antimicrobial agent or other added substance. The pH is between 4.5 and 7.0. Its chloride and sodium ion concentrates are approximately 0.154 mEq of each per milliliter and its calculated osmolality is 0.308 milliosmols per mL.

Sodium chloride occurs as colorless cubic crystals or white crystalline powder and has a saline taste. Sodium Chloride is freely soluble in water. It is soluble in glycerin and slightly soluble in alcohol. The empirical formula for sodium chloride is NaCl, and the molecular weight is 58.44.

CLINICAL PHARMACOLOGY
Sodium chloride comprises over 90% of the inorganic constituents of the blood serum. Sodium chloride in water dissociates to provide sodium (Na+) and (Cl-) ions. These ions are normal constituents of the body fluids (principally extracellular) and are essential for maintaining electrolyte balance. The small volume of fluid and amount of sodium chloride provided by Sodium Chloride Injection, USP, 0.9% when used only as a vehicle for parenteral injection of drugs, is unlikely to exert a significant effect on fluid and electrolyte balance except possibly in very small infants.

INDICATIONS AND USAGE
Sodium Chloride Injection is used to flush intravascular catheters or as a sterile, isontonic single dose vehicle, solvent, or diluent for substances to administered intravenously, intramuscularly or subcutaneously and for other extemporaneously prepared single dose sterile solutions according to instructions of the manufacture of the drug to be administered.

WARNING
Sodium Chloride must be used with caution in the presence of congestive heart failure, circulatory insufficiency, kidney dysfunction or hypoproteinemia. Excessive amounts of sodium chloride by any route may cause hypokalemia and acidosis. Excessive amounts by parental routes may precipitate congestive heart failure and acute pulmonary edema, especially seen in patients with preexisting cardiovascular disease and those receiving corticosteroids, corticotrophin or other drugs that may give rise to sodium retention. For use in newborns, when a Sodium Chloride solution is required for preparation or diluting medications, or in flushing intravenous catheters, only preservative-free Sodium Chloride Injection, USP, 0.9% should be used.

PRECAUTIONS
GENERAL
Since Sodium Chloride Injection does not contain antimicrobial agents and is intended for single use, any unused amount must be discarded immediately following withdrawal of any portion of the contents of the vial or ampul. Do not open ampul until it is to be used. Consult the manufactures instructions for choice of vehicle, appropriate dilution or volume for dissolving the drug to be injected, including the route and rate of injection.

PREGNANCY
CATEGORY C-Animal reproduction studies have not been conducted with Sodium Chloride Injection. It is also not known whether Sodium Chloride Injection can cause fetal harm when administered to a pregnant woman or can effect reproduction capacity. Sodium Chloride Injection should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS
Reactions which may occur because of this solution, added drugs or the technique of reconstitution or...
administration include febrile response, local tenderness, abscess, tissue necrosis or infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection and extravasations. If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate countermeasures and if possible, retrieve and save the remainder of unused vehicle for examination.

OVERDOSAGE
When used as a diluent, solvent or intravascular flushing solution, this parental preparation is unlikely to pose a threat of sodium chloride or fluid overload except possible in very small infants. In the event these should occur, reevaluate the patient and institute appropriate corrective measures.

DOSAGE AND ADMINISTRATION
Before Sodium Chloride Injection, USP, 0.9% is used as a vehicle for the administration of a drug; specific references should be checked for any possible incompatibility with sodium chloride. The volume of the preparation to be used for diluting or dissolving any drug for injection is dependent on the vehicle concentration, dose and route of administration as recommended by the manufacture. Sodium Chloride Injection, USP, 0.9% is also indicated for use in flushing intravenous catheters. Prior to and after administration of the medication, the intravenous catheter should be flushed in its entirety with Sodium Chloride Injection, USP, 0.9%. Use in accord with any warnings or precautions appropriate to the medication being administered as recommended by the manufacture. Parental drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED
5 mL ampuls packaged in box of 50 each (NDC-65282-1505-1)
10 mL ampuls packaged in box of 50 each (NDC-65282-1510-1)
30 mL ampuls packaged in box of 30 each (NDC-65282-1530-3)

STORAGE
Manufactured for:
Spectra Medical Devices, Inc. 260-F Fordham Road, Wilmington, MA 01887
By: KM. Pharm Co., LTD.

LIDOCAINE HYDROCHLORIDE AND EPINEPHRINE injection, solution
[Hospira, Inc.]
For Infiltration and Nerve Block.

Ampul
Fliptop Vial
Multiple-dose Fliptop Vial
Protect from light.
Rx only

DESCRIPTION
Lidocaine Hydrochloride and Epinephrine Injection, USP is a sterile, nonpyrogenic solution of lidocaine hydrochloride and epinephrine in water for injection for parenteral administration in various concentrations with characteristics as follows:

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Lidocaine HCl (anhyd.) mg/mL</th>
<th>Epinephrine mcg/mL</th>
<th>Sodium Chloride mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5%</td>
<td>1:200,000</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>1%</td>
<td>1:200,000</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>1.5%</td>
<td>1:200,000</td>
<td>15</td>
<td>6.5</td>
</tr>
<tr>
<td>2%</td>
<td>1:200,000</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>1%</td>
<td>1:100,000</td>
<td>10</td>
<td>7</td>
</tr>
</tbody>
</table>
Sodium metabisulfite 0.5 mg/mL and citric acid, anhydrous 0.2 mg/mL added as stabilizers. The headspace of Lists 1209, and 3179 are carbon dioxide gassed and Lists 3177, 3178, 3181, 3182 and 3183 are nitrogen gassed. May contain sodium hydroxide and/or hydrochloric acid to adjust pH; pH is 4.5 (3.3 to 5.5). See HOW SUPPLIED section for various sizes and strengths.

Multiple-dose vials contain methylparaben 1 mg/mL added as preservative.

Single-dose ampuls and vials contain no bacteriostat or antimicrobial agent. Discard unused portion.

Lidocaine is a local anesthetic of the amide type.

Lidocaine Hydrochloride, USP is chemically designated 2-(diethyl-amino)-2',6'-acetoxylidide monohydrochloride monohydrate, a white powder freely soluble in water. It has the following structural formula:

![Structural formula of Lidocaine](image)

Epinephrine, USP is a sympathomimetic (adrenergic) agent designated chemically as 4-[1-hydroxy-2 (methylamino) ethyl]-1,2 benzenediol, a white, microcrystalline powder. It has the following structural formula:

![Structural formula of Epinephrine](image)

**CLINICAL PHARMACOLOGY**

Mechanism of action: Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action.
Hemodynamics: Excessive blood levels may cause changes in cardiac output, total peripheral resistance, and mean arterial pressure. With central neural blockade these changes may be attributable to block of autonomic fibers, a direct depressant effect of the local anesthetic agent on various components of the cardiovascular system and/or the beta-adrenergic receptor stimulating action of epinephrine when present. The net effect is normally a modest hypotension when the recommended dosages are not exceeded.

Pharmacokinetics and metabolism: Information derived from diverse formulations, concentrations and usages reveals that lidocaine is completely absorbed following parenteral administration, its rate of absorption depending, for example, upon various factors such as the site of administration and the presence or absence of a vasoconstrictor agent. Except for intravascular administration, the highest blood levels are obtained following intercostal nerve block and the lowest after subcutaneous administration.

The plasma binding of lidocaine is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1 to 4 µg of free base per mL, 60 to 80 percent of lidocaine is protein bound. Binding is also dependent on the plasma concentration of the alpha-1-acid glycoprotein.

Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion. Lidocaine is metabolized rapidly by the liver, and metabolites and unchanged drug are excreted by the kidneys. Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. N-dealkylation, a major pathway of biotransformation, yields the metabolites monoethylglycinexylidide and glycinexylidide. The pharmacological/toxicological actions of these metabolites are similar to, but less potent than, those of lidocaine. Approximately 90% of lidocaine administered is excreted in the form of various metabolites, and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2, 6-dimethylaniline.

The elimination half-life of lidocaine following an intravenous bolus injection is typically 1.5 to 2.0 hours. Because of the rapid rate at which lidocaine is metabolized, any condition that affects liver function may alter lidocaine kinetics. The half-life may be prolonged two-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.

Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lidocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6.0 µg free base per mL. In the rhesus monkey arterial blood levels of 18-21 µg/mL have been shown to be threshold for convulsive activity.

INDICATIONS AND USAGE
Lidocaine Hydrochloride and Epinephrine Injection, USP is indicated for production of local or regional anesthesia by infiltration techniques such as percutaneous injection, by peripheral nerve block techniques such as brachial plexus and intercostal and by central neural techniques such as lumbar and caudal epidural blocks, when the accepted procedures for these techniques as described in standard textbooks are observed.

CONTRAINDICATIONS
Lidocaine is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type.

WARNINGS
LIDOCAINE HYDROCHLORIDE AND EPINEPHRINE INJECTION, USP FOR INFILTRATION AND NERVE BLOCK SHOULD BE EMPLOYED ONLY BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES THAT MIGHT ARISE FROM THE BLOCK TO BE Employed AND THEN ONLY AFTER ENSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY EQUIPMENT, AND THE PERSONNEL NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED
EMERGENCIES (See also ADVERSE REACTIONS and PRECAUTIONS). DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of gleno-humeral chondrolysis have been described in pediatric and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. The time of onset of symptoms, such as joint pain, stiffness and loss of motion can be variable, but may begin as early as the 2nd month after surgery. Currently, there is no effective treatment for chondrolysis; patients who experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

To avoid intravascular injection, aspiration should be performed before the local anesthetic solution is injected. The needle must be repositioned until no return of blood can be elicited by aspiration. Note, however, that the absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

Local anesthetic solutions containing antimicrobial preservatives (e.g., methylparaben) should not be used for epidural or spinal anesthesia because the safety of these agents has not been established with regard to intrathecal injection, either intentional or accidental.

Lidocaine Hydrochloride and Epinephrine Injection contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

General: The safety and effectiveness of lidocaine depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Standard textbooks should be consulted for specific techniques and precautions for various regional anesthetic procedures.

Resuscitative equipment, oxygen, and other 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 levels and serious adverse effects. Syringe aspirations should also be performed before and during each supplemental injection when using indwelling catheter techniques. During the administration of epidural anesthesia, it is recommended that a test dose be administered initially and that the patient be monitored for central nervous system toxicity 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. Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose because of slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients and children should be given reduced doses commensurate with their age and physical condition. Lidocaine should also be used with caution in patients with severe shock or heart block.

Lumbar and caudal epidural anesthesia should be used with extreme caution in persons with the following conditions: existing neurological disease, spinal deformities, septicemia and severe hypertension.

Local anesthetic solutions containing a vasoconstrictor should be used cautiously and in carefully circumscribed quantities in areas of the body supplied by end arteries or having otherwise compromised blood supply. Patients with peripheral vascular disease and those with hypertensive
vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result. Preparations containing a vasoconstrictor should be used with caution in patients during or following the administration of potent general anesthetic agents, since cardiac arrhythmias may occur under such conditions.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient’s state of consciousness should be accomplished after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity. Since amide-type local anesthetics are metabolized by the liver, lidocaine injection should be used with caution in patients with hepatic disease. Patients with severe hepatic disease because of their inability to metabolize local anesthetics normally, are a greater risk of developing toxic plasma concentrations. Lidocaine should also be used with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Since it is not known whether amide-type local anesthetics may trigger this reaction and since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for the management of malignant hyperthermia should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene (consult dantrolene sodium intravenous package insert before using).

Injections containing epinephrine or other vasoconstrictors should not be used for intravenous regional anesthesia.

Lidocaine should be used with caution in persons with known drug sensitivities. Patients allergic to para-amino-benzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

Use in the Head and Neck Area: Small doses of local anesthetics injected into the head and neck area, including retrobulbar, dental and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression and/or respiratory arrest and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injections of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration 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, usually in the lower half of the body following proper administration of epidural anesthesia.

Clinically Significant Drug Interactions: The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe prolonged hypertension. Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential. Concurrent administration of vasopressor drugs (for the treatment of hypotension related to obstetric blocks) and ergot-type oxytocic drugs may cause severe persistent hypertension or cerebrovascular accidents.

Drug Laboratory Test Interactions: The intramuscular injection of lidocaine may result in an increase in creatine phosphokinase levels. Thus, the use of this enzyme determination without isoenzyme separation as a diagnostic test for the presence of acute myocardial infarction may be compromised by the intramuscular injection of lidocaine.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies of lidocaine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Pregnancy: Teratogenic Effects. Pregnancy Category B. Reproduction studies have been performed in rats at doses up to 6.6 times the human dose and have revealed no evidence of harm to the fetus caused by lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response. General consideration should be given to this fact before administering lidocaine to women of childbearing potential, especially during early pregnancy when maximum organogenesis takes place.

Labor and Delivery: Local anesthetics rapidly cross the placenta and when used for epidural, paracervical, pudendal or caudal block anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity (See CLINICAL PHARMACOLOGY-Pharmacokinetics). The potential for toxicity depends 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 has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously, and electronic fetal monitoring is highly advisable.

Epidural, spinal, paracervical, or pudendal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. In one study, paracervical block anesthesia was associated with a decrease in the mean duration of first stage labor and facilitation of cervical dilation. However, spinal and epidural anesthesia have also been reported to prolong the second stage of labor by removing the parturient’s reflex urge to bear down or by interfering with motor function. The use of obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may be followed by diminished muscle strength and tone for the first day or two of life. The long term significance of these observations is unknown. Fetal bradycardia may occur in 20 to 30 percent of patients receiving paracervical nerve block anesthesia with the amide-type local anesthetics and may be associated with fetal acidosis. Fetal heart rate should always be monitored during paracervical anesthesia. The physician should weigh the possible advantages against risks when considering paracervical block in prematurity, toxemia of pregnancy and fetal distress. Careful adherence to recommended dosage is of utmost importance in obstetrical paracervical block. Failure to achieve adequate analgesia with recommended doses should arouse suspicion of intravascular or fetal intracranial injection. Cases compatible with unintended fetal intracranial injection of local anesthetic solution have been reported following intended paracervical or pudendal block or both. Babies so affected present with unexplained neonatal depression at birth, which correlates with high local anesthetic serum levels, and often manifest seizures within six hours. Prompt use of supportive measures combined with forced urinary excretion of the local anesthetic has been used successfully to manage this complication.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lidocaine is administered to a nursing woman.

Pediatric Use: Dosages in pediatric patients should be reduced, commensurate with age, body weight and physical condition. See DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS

Systemic: Adverse experiences following the administration of lidocaine are similar in nature to those observed with other amide local anesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by excessive dosage, rapid absorption or inadvertent intravascular injection, or may result from a hypersensitivity, idiosyncrasy or diminished
tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature. The following types are those most commonly reported:

Central Nervous System: CNS manifestations are excitatory and/or depressant and may be characterized by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest. The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest.

Drowsiness following the administration of lidocaine is usually an early sign of a high blood level of the drug and may occur as a consequence of rapid absorption.

Cardiovascular System: Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

Allergic: Allergic reactions are characterized by cutaneous lesions, urticaria, edema or anaphylactoid reactions. Allergic reactions may occur as a result of sensitivity either to local anesthetic agents, to bisulfites or to the methylparaben used as a preservative in multiple dose vials. Allergic reactions as a result of sensitivity to lidocaine are extremely rare and, if they occur, should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Neurologic: The incidences of adverse reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon the particular drug used, the route of administration and the physical status of the patient. In a prospective review of 10,440 patients who received lidocaine for spinal anesthesia, the incidences of adverse reactions were reported to be about 3 percent each for positional headaches, hypotension and backache; 2 percent for shivering; and less than 1 percent each for peripheral nerve symptoms, nausea, respiratory inadequacy and double vision. Many of these observations may be related to local anesthetic techniques, with or without a contribution from the local anesthetic.

In the practice of caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter may occur. Subsequent adverse effects may depend partially on the amount of drug administered subdurally. These may include spinal block of varying magnitude (including total spinal block), hypotension secondary to spinal block, loss of bladder and bowel control, and loss of perineal sensation and sexual function. Persistent motor, sensory and/or autonomic (sphincter control) deficit of some lower spinal segments with slow recovery (several months) or incomplete recovery have been reported in rare instances when caudal or lumbar epidural block has been attempted. Backache and headache have also been noted following use of these anesthetic procedures.

There have been reported cases of permanent injury to extraocular muscles requiring surgical repair following retrobulbar administration.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid injection of local anesthetic solution (see ADVERSE REACTIONS, WARNINGS and PRECAUTIONS).

Management of Local Anesthetic Emergencies: The first consideration is prevention, best accomplished by careful monitoring of cardiovascular and respiratory vital signs and the patient’s state of consciousness after each local anesthetic injection. At the first sign of change, oxygen should be administered.

The first step in the management of convulsions, as well as under-ventilation or apnea due to unintended subarachnoid injection of drug solution, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat
convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to use of local anesthetics, with these anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., ephedrine).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. Underventilation or apnea due to unintentional subarachnoid injection of local anesthetic solution may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest should occur standard cardiopulmonary resuscitative measures should be instituted.

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

Dialysis is of negligible value in the treatment of acute overdosage with lidocaine.

The oral LD50 of lidocaine HCl in non-fasted female rats is 459 (346-773) mg/kg (as the salt) and 214 (159-324) mg/kg (as the salt) in fasted female rats.

DOSAGE AND ADMINISTRATION

Table I (Recommended Dosages) summarizes the recommended volumes and concentrations of Lidocaine Hydrochloride Injection, USP for various types of anesthetic procedures. The dosages suggested in this table are for normal healthy adults and refer to the use of epinephrine-free solutions. When larger volumes are required only solutions containing epinephrine should be used, except in those cases where vasopressor drugs may be contraindicated.

There have been adverse event reports of chondrolysis in patients receiving intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures. Lidocaine is not approved for this use (see WARNINGS and DOSAGE AND ADMINISTRATION).

These recommended doses serve only as a guide to the amount of anesthetic required for most routine procedures. The actual volumes and concentrations to be used depend on a number of factors such as type and extent of surgical procedure, depth of anesthesia and degree of muscular relaxation required, duration of anesthesia required, and the physical condition of the patient. In all cases the lowest concentration and smallest dose that will produce the desired result should be given. Dosages should be reduced for children and for elderly and debilitated patients and patients with cardiac and/or liver disease.

The onset of anesthesia, the duration of anesthesia and the degree of muscular relaxation are proportional to the volume and concentration (i.e., total dose) of local anesthetic used. Thus, an increase in volume and concentration of Lidocaine Hydrochloride Injection, USP will decrease the onset of anesthesia, prolong the duration of anesthesia, provide a greater degree of muscular relaxation and increase the segmental spread of anesthesia. However, increasing the volume and concentration of Lidocaine Hydrochloride Injection, USP may result in a more profound fall in blood pressure when used in epidural anesthesia. Although the incidence of side effects with lidocaine is quite low, caution should be exercised when employing large volumes and concentrations, since the incidence of side effects is directly proportional to the total dose of local anesthetic agent injected.

Epidural Anesthesia

For an epidural test dose, only the following available specific product of Lidocaine Hydrochloride and Epinephrine Injection, USP by Hospira is recommended:

1.5% with epinephrine 1:200,000................. 5 mL single-dose ampuls
For epidural anesthesia, only the following available specific products of Lidocaine Hydrochloride and Epinephrine Injection, USP by Hospira are recommended:

1% with epinephrine 1:200,000............................ 30 mL single-dose ampuls
30 mL single-dose vials
1.5% with epinephrine 1:200,000.......................... 30 mL single-dose ampuls
30 mL single-dose vials
2% with epinephrine 1:200,000................................ 20 mL single-dose vials

Although these solutions are intended specifically for epidural anesthesia, they may also be used for infiltration and peripheral nerve block provided they are employed as single-dose units. These solutions contain no bacteriostatic agent.

In epidural anesthesia, the dosage varies with the number of dermatomes to be anesthetized (generally 2-3 mL of the indicated concentration per dermatome). Caudal and Lumbar Epidural Block: As a precaution against the adverse experiences sometimes observed following unintentional penetration of the subarachnoid space, a test dose such as 2-3 mL of 1.5% lidocaine injection should be administered at least 5 minutes prior to injecting the total volume required for a lumbar or caudal epidural block. The test dose should be repeated if the patient is moved in a manner that may have displaced the catheter. Epinephrine, if contained in the test dose (10-15 µg have been suggested), may serve as a warning of unintentional intravascular injection. If injected into a blood vessel, this amount of epinephrine is likely to produce a transient “epinephrine response” within 45 seconds, consisting of an increase in heart rate and systolic blood pressure, circumoral pallor, palpitations and nervousness in the unsedated patient. The sedated patient may exhibit only a pulse rate increase of 20 or more beats per minute for 15 or more seconds. Patients on beta-blockers may not manifest changes in heart rate, but blood pressure monitoring can detect an evanescent rise in systolic blood pressure. Adequate time should be allowed for onset of anesthesia after administration of each test dose. The rapid injection of a large volume of Lidocaine Hydrochloride and Epinephrine Injection, USP through the catheter should be avoided, and, when feasible, fractional doses should be administered. In the event of the known injection of a large volume of local anesthetic solution into the subarachnoid space, after suitable resuscitation and if the catheter is in place, consider attempting the recovery of drug by draining a moderate amount of cerebrospinal fluid (such as 10 mL) through the epidural catheter.

Maximum Recommended Dosages

Adults: For normal healthy adults, the individual maximum dose of Lidocaine Hydrochloride and Epinephrine Injection, USP should not exceed 7 mg/kg (3.5 mg/lb) of body weight and in general it is recommended that the maximum total dose not exceed 500 mg. When used without epinephrine, the maximum individual dose should not exceed 4.5 mg/kg (2 mg per lb) of body weight, and in general it is recommended that the maximum total dose does not exceed 300 mg. For continuous epidural or caudal anesthesia, the maximum recommended dosage should not be administered at intervals of less than 90 minutes. When continuous lumbar or caudal epidural anesthesia is used for non-obstetrical procedures, more drug may be administered if required to produce adequate anesthesia.

The maximum recommended dose per 90 minute period of lidocaine hydrochloride for paracervical block in obstetrical patients and non-obstetrical patients is 200 mg total. One half of the total dose is usually administered to each side. Inject slowly five minutes between sides. (See also discussion of paracervical block in PRECAUTIONS).

Pediatric Population: It is difficult to recommend a maximum dose of any drug for pediatric patients, since this varies as a function of age and weight. For pediatric patients over 3 years of age who have a normal lean body mass and normal body development, the maximum dose is determined by the child’s
age and weight. For example, in a child of 5 years weighing 50 lbs., the dose of lidocaine HCl should not exceed 75-100 mg (1.5-2 mg/lb).

In order to guard against systemic toxicity, the lowest effective concentration and lowest effective dose should be used at all times. In some cases it will be necessary to dilute available concentrations with 0.9% sodium chloride injection in order to obtain the required final concentration.

FOR EPIDURAL USE ONLY.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. Do not use the injection if its color is pinkish or darker than slightly yellow or if it contains a precipitate.

Table I Recommended Dosages of Lidocaine Hydrochloride Injection, USP for Various Anesthetic Procedures in Normal Healthy Adults

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Lidocaine Hydrochloride Injection, USP (without Epinephrine)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conc. (%)</td>
</tr>
<tr>
<td>Infiltration</td>
<td></td>
</tr>
<tr>
<td>Percutaneous</td>
<td>0.5 or 1.0</td>
</tr>
<tr>
<td>Intravenous Regional</td>
<td>0.5</td>
</tr>
<tr>
<td>Peripheral Nerve Blocks, e.g.</td>
<td></td>
</tr>
<tr>
<td>Brachial</td>
<td>1.5</td>
</tr>
<tr>
<td>Dental</td>
<td>2.0</td>
</tr>
<tr>
<td>Intercostal</td>
<td>1.0</td>
</tr>
<tr>
<td>Paravertebral</td>
<td>1.0</td>
</tr>
<tr>
<td>Pudendal (each side)</td>
<td>1.0</td>
</tr>
<tr>
<td>Paracervical Obstetrical Analgesia (each side)</td>
<td>1.0</td>
</tr>
<tr>
<td>Sympathetic Nerve Blocks, e.g.</td>
<td></td>
</tr>
<tr>
<td>Cervical (stellate ganglion)</td>
<td>1.0</td>
</tr>
<tr>
<td>Lumbar</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Central Neural Blocks</td>
<td></td>
</tr>
<tr>
<td>Epidural*</td>
<td></td>
</tr>
<tr>
<td>Thoracic</td>
<td>1.0</td>
</tr>
<tr>
<td>Lumbar</td>
<td>1.0</td>
</tr>
<tr>
<td>Analgesia</td>
<td>1.5</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>2.0</td>
</tr>
<tr>
<td>Caudal</td>
<td></td>
</tr>
<tr>
<td>Obstetrical Analgesia</td>
<td>1.0</td>
</tr>
<tr>
<td>Surgical Anesthesia</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*Dose determined by number of dermatomes to be anesthetized (2 to 3 mL/dermatome).

THE ABOVE SUGGESTED CONCENTRATIONS AND VOLUMES SERVE ONLY AS A GUIDE.
OTHER VOLUMES AND CONCENTRATIONS MAY BE USED PROVIDED THE TOTAL MAXIMUM RECOMMENDED DOSE IS NOT EXCEEDED.

Sterilization, Storage and Technical Procedures: Disinfecting agents containing heavy metals, which cause release of respective ions (mercury, zinc, copper, etc.) should not be used for skin or mucous membrane disinfection as they have been related to incidence of swelling and edema. When chemical disinfection of multi-dose vials is desired, either isopropyl alcohol (91%) or 70% ethyl alcohol is recommended. Many commercially available brands of rubbing alcohol, as well as solutions of ethyl alcohol not of USP grade, contain denaturants which are injurious to rubber and, therefore, are not to be used. It is recommended that chemical disinfection be accomplished by wiping the vial stopper or ampul thoroughly with cotton or gauze that has been moistened with the recommended alcohol just prior to use.

Do not autoclave.

HOW SUPPLIED

Lidocaine Hydrochloride and Epinephrine Injection, USP is supplied in single-dose and multiple-dose containers as shown below:

<table>
<thead>
<tr>
<th>No.</th>
<th>Container</th>
<th>Size</th>
<th>Drug Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lidocaine HCl</td>
<td>Epinephrine</td>
<td></td>
</tr>
<tr>
<td>Single-dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0409-3181-01</td>
<td>Fliptop Vial</td>
<td>30 mL</td>
<td>1.5%</td>
</tr>
<tr>
<td>0409-3183-01</td>
<td>Fliptop Vial</td>
<td>20 mL</td>
<td>2%</td>
</tr>
<tr>
<td>Epidural Test Dose (single-dose)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0409-1209-01</td>
<td>Ampul</td>
<td>5 mL</td>
<td>1.5%</td>
</tr>
<tr>
<td>0409-1209-05</td>
<td>Ampul</td>
<td>5 mL</td>
<td>1.5%</td>
</tr>
<tr>
<td>0409-1209-65</td>
<td>Ampul</td>
<td>5 mL</td>
<td>1.5%</td>
</tr>
<tr>
<td>Multiple-dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0409-3177-01</td>
<td>Fliptop Vial</td>
<td>50 mL</td>
<td>0.5%</td>
</tr>
<tr>
<td>0409-3178-01</td>
<td>Fliptop Vial</td>
<td>20 mL</td>
<td>1%</td>
</tr>
<tr>
<td>0409-3178-02</td>
<td>Fliptop Vial</td>
<td>30 mL</td>
<td>1%</td>
</tr>
<tr>
<td>0409-3178-03</td>
<td>Fliptop Vial</td>
<td>50 mL</td>
<td>1%</td>
</tr>
<tr>
<td>0409-3182-01</td>
<td>Fliptop Vial</td>
<td>20 mL</td>
<td>2%</td>
</tr>
<tr>
<td>0409-3182-02</td>
<td>Fliptop Vial</td>
<td>30 mL</td>
<td>2%</td>
</tr>
<tr>
<td>0409-3182-03</td>
<td>Fliptop Vial</td>
<td>50 mL</td>
<td>2%</td>
</tr>
</tbody>
</table>

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.] Protect from light.

Revised: March, 2010
Printed in USA EN-2440
Hospira, Inc., Lake Forest, IL 60045 USA
Package Label Display Panel
Lidocaine Hydrochloride Injection, USP is a sterile, nonpyrogenic solution of lidocaine hydrochloride in water for injection for parenteral administration in various concentrations with characteristics as follows:
Concentration | 0.5% | 1% | 1.5% | 2%
--- | --- | --- | --- | ---
mg/mL lidocaine HCl (anhyd.) | 5 | 10 | 15 | 20
mg/mL sodium chloride | 8 | 7 | 6.5 | 6

Multiple-dose vials contain 0.1% of methylparaben added as preservative. May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. The pH is 6.5 (5.0 to 7.0). See HOW SUPPLIED section for various sizes and strengths.

Lidocaine is a local anesthetic of the amide type.

Lidocaine Hydrochloride, USP is chemically designated 2-(diethylamino)-N-(2,6-dimethylphenyl)-acetamide monohydrochloride monohydrate, a white powder freely soluble in water. The molecular weight is 288.82. It has the following structural formula:

![Structural formula of Lidocaine](image)

The semi-rigid vial used for the plastic vials is fabricated from a specially formulated polyolefin. It is a copolymer of ethylene and propylene. The safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers. The container requires no vapor barrier to maintain the proper drug concentration.

**CLINICAL PHARMACOLOGY**

**Mechanism of action:** Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action.

**Hemodynamics:** Excessive blood levels may cause changes in cardiac output, total peripheral resistance, and mean arterial pressure. With central neural blockade these changes may be attributable to block of autonomic fibers, a direct depressant effect of the local anesthetic agent on various components of the cardiovascular system and/or the beta-adrenergic receptor stimulating action of epinephrine when present. The net effect is normally a modest hypotension when the recommended dosages are not exceeded.

**Pharmacokinetics and metabolism:** Information derived from diverse formulations, concentrations and usages reveals that lidocaine is completely absorbed following parenteral administration, its rate of absorption depending, for example, upon various factors such as the site of administration and the presence or absence of a vasoconstrictor agent. Except for intravascular administration, the highest blood levels are obtained following intercostal nerve block and the lowest after subcutaneous administration.

The plasma binding of lidocaine is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1 to 4 mcg of free base per mL, 60 to 80 percent of lidocaine is protein bound. Binding is also dependent on the plasma concentration of the alpha-1-acid glycoprotein.

Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion.

Lidocaine is metabolized rapidly by the liver, and metabolites and unchanged drug are excreted by the kidneys. Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. N-dealkylation, a major pathway of biotransformation, yields the metabolites
monoethylglycinexylidide and glycinexylidide. The pharmacological/toxicological actions of these metabolites are similar to, but less potent than, those of lidocaine. Approximately 90% of lidocaine administered is excreted in the form of various metabolites, and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2, 6-dimethylaniline.

The elimination half-life of lidocaine following an intravenous bolus injection is typically 1.5 to 2.0 hours. Because of the rapid rate at which lidocaine is metabolized, any condition that affects liver function may alter lidocaine kinetics. The half-life may be prolonged two-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.

Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lidocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6.0 mcg free base per mL. In the rhesus monkey arterial blood levels of 18-21 mcg/mL have been shown to be threshold for convulsive activity.

INDICATIONS AND USAGE

Lidocaine Hydrochloride Injection, USP is indicated for production of local or regional anesthesia by infiltration techniques such as percutaneous injection and intravenous regional anesthesia by peripheral nerve block techniques such as brachial plexus and intercostal and by central neural techniques such as lumbar and caudal epidural blocks, when the accepted procedures for these techniques as described in standard textbooks are observed.

CONTRAINDICATIONS

Lidocaine is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type.

WARNINGS

LIDOCAINE HYDROCHLORIDE INJECTION, FOR INFILTRATION AND NERVE BLOCK, SHOULD BE EMPLOYED ONLY BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES THAT MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED AND THEN ONLY AFTER ENSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY EQUIPMENT, AND THE PERSONNEL NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES (See also ADVERSE REACTIONS and PRECAUTIONS). DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of gleno-humeral chondrolysis have been described in pediatric and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. The time of onset of symptoms, such as joint pain, stiffness and loss of motion can be variable, but may begin as early as the 2nd month after surgery. Currently, there is no effective treatment for chondrolysis; patients who experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

To avoid intravascular injection, aspiration should be performed before the local anesthetic solution is injected. The needle must be repositioned until no return of blood can be elicited by aspiration. Note, however, that the absence of blood in the syringe does not guarantee that intravascular injection has
been avoided.

Local anesthetic solutions containing antimicrobial preservatives (e.g., methylparaben) should not be used for epidural or spinal anesthesia because the safety of these agents has not been established with regard to intrathecal injection, either intentional or accidental.

PRECAUTIONS

General:

The safety and effectiveness of lidocaine depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Standard textbooks should be consulted for specific techniques and precautions for various regional anesthetic procedures.

Resuscitative equipment, oxygen, and other 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 levels and serious adverse effects. Syringe aspirations should also be performed before and during each supplemental injection when using indwelling catheter techniques. During the administration of epidural anesthesia, it is recommended that a test dose be administered initially and that the patient be monitored for central nervous system toxicity 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. Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose because of slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients and children should be given reduced doses commensurate with their age and physical condition. Lidocaine should also be used with caution in patients with severe shock or heart block. Lumbar and caudal epidural anesthesia should be used with extreme caution in persons with the following conditions: existing neurological disease, spinal deformities, septicemia and severe hypertension.

Local anesthetic solutions containing a vasoconstrictor should be used cautiously and in carefully circumscribed quantities in areas of the body supplied by end arteries or having otherwise compromised blood supply. Patients with peripheral vascular disease and those with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result. Preparations containing a vasoconstrictor should be used with caution in patients during or following the administration of potent general anesthetic agents, since cardiac arrhythmias may occur under such conditions.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient’s state of consciousness should be accomplished after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity.

Since amide-type local anesthetics are metabolized by the liver, lidocaine should be used with caution in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations. Lidocaine should also be used with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs. Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Since it is not known whether amide-type local anesthetics may trigger this reaction and since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for the management of malignant hyperthermia should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure and metabolic acidosis may precede temperature elevation. Successful outcome is dependent
on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene (consult dantrolene sodium intravenous package insert before using).

Proper tourniquet technique, as described in publications and standard textbooks, is essential in the performance of intravenous regional anesthesia. Solutions containing epinephrine or other vasoconstrictors should not be used for this technique.

Lidocaine should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

Use in the Head and Neck Area: Small doses of local anesthetics injected into the head and neck area, including retrobulbar, dental and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression and/or respiratory arrest and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injections of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration 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, usually in the lower half of the body following proper administration of epidural anesthesia.

Clinically Significant Drug Interactions:

The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe prolonged hypertension.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs (for the treatment of hypotension related to obstetric blocks) and ergot-type oxytocic drugs may cause severe persistent hypertension or cerebrovascular accidents.

Drug Laboratory Test Interactions:

The intramuscular injection of lidocaine may result in an increase in creatine phosphokinase levels. Thus, the use of this enzyme determination without isoenzyme separation as a diagnostic test for the presence of acute myocardial infarction may be compromised by the intramuscular injection of lidocaine.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Studies of lidocaine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Pregnancy:

Teratogenic Effects. Pregnancy Category B. Reproduction studies have been performed in rats at doses up to 6.6 times the human dose and have revealed no evidence of harm to the fetus caused by lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response. General consideration should be given to this fact before administering lidocaine to women of childbearing potential, especially during early pregnancy.
when maximum organogenesis takes place.

Labor and Delivery:

Local anesthetics rapidly cross the placenta and when used for epidural, paracervical, pudendal or caudal block anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity (See CLINICAL PHARMACOLOGY—Pharmacokinetics). The potential for toxicity depends 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 has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient’s legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously, and electronic fetal monitoring is highly advisable.

Epidural, spinal, paracervical, or pudendal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. In one study, paracervical block anesthesia was associated with a decrease in the mean duration of first stage labor and facilitation of cervical dilation. However, spinal and epidural anesthesia have also been reported to prolong the second stage of labor by removing the parturient’s reflex urge to bear down or by interfering with motor function. The use of obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may be followed by diminished muscle strength and tone for the first day or two of life. The long-term significance of these observations is unknown. Fetal bradycardia may occur in 20 to 30 percent of patients receiving paracervical nerve block anesthesia with the amide-type local anesthetics and may be associated with fetal acidosis. Fetal heart rate should always be monitored during paracervical anesthesia. The physician should weigh the possible advantages against risks when considering paracervical block in prematurity, toxemia of pregnancy and fetal distress. Careful adherence to recommended dosage is of the utmost importance in obstetrical paracervical block. Failure to achieve adequate analgesia with recommended doses should arouse suspicion of intravascular or fetal intracranial injection. Cases compatible with unintended fetal intracranial injection of local anesthetic solution have been reported following intended paracervical or pudendal block or both. Babies so affected present with unexplained neonatal depression at birth, which correlates with high local anesthetic serum levels, and often manifest seizures within six hours. Prompt use of supportive measures combined with forced urinary excretion of the local anesthetic has been used successfully to manage this complication.

Case reports of maternal convulsions and cardiovascular collapse following use of some local anesthetics for paracervical block in early pregnancy (as anesthesia for elective abortion) suggest that systemic absorption under these circumstances may be rapid. The recommended maximum dose of each drug should not be exceeded. Injection should be made slowly and with frequent aspiration. Allow a 5-minute interval between sides.

Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lidocaine is administered to a nursing woman.

Pediatric Use:

Dosages in pediatric patients should be reduced, commensurate with age, body weight and physical condition. See DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS

Systemic: Adverse experiences following the administration of lidocaine are similar in nature to those observed with other amide local anesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by excessive dosage, rapid absorption or
inadvertent intravascular injection, or may result from a hypersensitivity, idiosyncrasy or diminished
tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature. The
following types are those most commonly reported:

Central Nervous System: CNS manifestations are excitatory and/or depressant and may be characterized
by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus,
blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors,
convulsions, unconsciousness, respiratory depression and arrest. The excitatory manifestations may be
very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness
merging into unconsciousness and respiratory arrest.

Drowsiness following the administration of lidocaine is usually an early sign of a high blood level of
the drug and may occur as a consequence of rapid absorption.

Cardiovascular System: Cardiovascular manifestations are usually depressant and are characterized
by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

Allergic: Allergic reactions are characterized by cutaneous lesions, urticaria, edema or anaphylactoid
reactions. Allergic reactions may occur as a result of sensitivity either to local anesthetic agents or to
the methylparaben used as a preservative in multiple dose vials. Allergic reactions as a result of
sensitivity to lidocaine are extremely rare and, if they occur, should be managed by conventional means.
The detection of sensitivity by skin testing is of doubtful value.

Neurologic: The incidences of adverse reactions associated with the use of local anesthetics may be
related to the total dose of local anesthetic administered and are also dependent upon the particular drug
used, the route of administration and the physical status of the patient. In a prospective review of 10,440
patients who received lidocaine for spinal anesthesia, the incidences of adverse reactions were
reported to be about 3 percent each for positional headaches, hypotension and backache; 2 percent for
shivering; and less than 1 percent each for peripheral nerve symptoms, nausea, respiratory inadequacy
and double vision. Many of these observations may be related to local anesthetic techniques, with or
without a contribution from the local anesthetic.

In the practice of caudal or lumbar epidural block, occasional unintentional penetration of the
subarachnoid space by the catheter may occur. Subsequent adverse effects may depend partially on the
amount of drug administered subdurally.

These may include spinal block of varying magnitude (including total spinal block), hypotension
secondary to spinal block, loss of bladder and bowel control, and loss of perineal sensation and sexual
function. Persistent motor, sensory and/or autonomic (sphincter control) deficit of some lower spinal
segments with slow recovery (several months) or incomplete recovery have been reported in rare
instances when caudal or lumbar epidural block has been attempted. Backache and headache have also
been noted following use of these anesthetic procedures.

There have been reported cases of permanent injury to extraocular muscles requiring surgical repair
following retrobulbar administration.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered
during therapeutic use of local anesthetics or to unintended subarachnoid injection of local anesthetic
solution (see ADVERSE REACTIONS, WARNINGS and PRECAUTIONS).

Management of Local Anesthetic Emergencies: The first consideration is prevention, best
accomplished by careful monitoring of cardiovascular and respiratory vital signs and the patient’s state
of consciousness after each local anesthetic injection. At the first sign of change, oxygen should be
administered.

The first step in the management of convulsions, as well as underventilation or apnea due to unintended
subarachnoid injection of drug solution, consists of immediate attention to the maintenance of a patent
airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to use of local anesthetics, with these anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., ephedrine).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. Underventilation or apnea due to unintentional subarachnoid injection of local anesthetic solution may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest should occur standard cardiopulmonary resuscitative measures should be instituted.

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

Dialysis is of negligible value in the treatment of acute overdosage with lidocaine.

The oral LD50 of lidocaine HCl in non-fasted female rats is 459 (346–773) mg/kg (as the salt) and 214 (159–324) mg/kg (as the salt) in fasted female rats.

DOSAGE AND ADMINISTRATION

Table 1 (Recommended Dosages) summarizes the recommended volumes and concentrations of Lidocaine Hydrochloride Injection, USP for various types of anesthetic procedures. The dosages suggested in this table are for normal healthy adults and refer to the use of epinephrine-free solutions. When larger volumes are required only solutions containing epinephrine should be used, except in those cases where vasopressor drugs may be contraindicated.

There have been adverse event reports of chondrolysis in patients receiving intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures. Lidocaine is not approved for this use (see WARNINGS and DOSAGE AND ADMINISTRATION).

These recommended doses serve only as a guide to the amount of anesthetic required for most routine procedures. The actual volumes and concentrations to be used depend on a number of factors such as type and extent of surgical procedure, depth of anesthesia and degree of muscular relaxation required, duration of anesthesia required, and the physical condition of the patient. In all cases the lowest concentration and smallest dose that will produce the desired result should be given. Dosages should be reduced for children and for elderly and debilitated patients and patients with cardiac and/or liver disease.

The onset of anesthesia, the duration of anesthesia and the degree of muscular relaxation are proportional to the volume and concentration (i.e., total dose) of local anesthetic used. Thus, an increase in volume and concentration of Lidocaine Hydrochloride Injection will decrease the onset of anesthesia, prolong the duration of anesthesia, provide a greater degree of muscular relaxation and increase the segmental spread of anesthesia. However, increasing the volume and concentration of Lidocaine Hydrochloride Injection may result in a more profound fall in blood pressure when used in epidural anesthesia. Although the incidence of side effects with lidocaine is quite low, caution should be exercised when employing large volumes and concentrations, since the incidence of side effects is directly proportional to the total dose of local anesthetic agent injected.

For intravenous regional anesthesia, only the 50 mL single-dose vial containing 0.5% Lidocaine Hydrochloride Injection, USP should be used.
Epidural Anesthesia

For epidural anesthesia, only the following available specific products of Lidocaine Hydrochloride Injection by Hospira are recommended:

1% ........................ 30 mL single-dose teartop vials
1.5% ........................ 20 mL single-dose ampuls
2% ........................ 10 mL single-dose ampuls

Although these solutions are intended specifically for epidural anesthesia, they may also be used for infiltration and peripheral nerve block provided they are employed as single dose units. These solutions contain no bacteriostatic agent. In epidural anesthesia, the dosage varies with the number of dermatomes to be anesthetized (generally 2–3 mL of the indicated concentration per dermatome).

Caudal and Lumbar Epidural Block: As a precaution against the adverse experiences sometimes observed following unintentional penetration of the subarachnoid space, a test dose such as 2–3 mL of 1.5% lidocaine hydrochloride should be administered at least 5 minutes prior to injecting the total volume required for a lumbar or caudal epidural block. The test dose should be repeated if the patient is moved in a manner that may have displaced the catheter. Epinephrine, if contained in the test dose (10–15 mcg have been suggested), may serve as a warning of unintentional intravascular injection. If injected into a blood vessel, this amount of epinephrine is likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and systolic blood pressure, circumoral pallor, palpitations and nervousness in the unsedated patient. The sedated patient may exhibit only a pulse rate increase of 20 or more beats per minute for 15 or more seconds. Patients on beta-blockers may not manifest changes in heart rate, but blood pressure monitoring can detect an evanescent rise in systolic blood pressure. Adequate time should be allowed for onset of anesthesia after administration of each test dose. The rapid injection of a large volume of Lidocaine Hydrochloride Injection through the catheter should be avoided, and, when feasible, fractional doses should be administered.

In the event of the known injection of a large volume of local anesthetic solutions into the subarachnoid space, after suitable resuscitation and if the catheter is in place, consider attempting the recovery of drug by draining a moderate amount of cerebrospinal fluid (such as 10 mL) through the epidural catheter.

Maximum Recommended Dosages

NOTE: The products accompanying this insert do not contain epinephrine.

Adults: For normal healthy adults, the individual maximum recommended dose of lidocaine HCl with epinephrine should not exceed 7 mg/kg (3.5 mg/lb) of body weight and in general it is recommended that the maximum total dose not exceed 500 mg. When used without epinephrine, the maximum individual dose should not exceed 4.5 mg/kg (2 mg/lb) of body weight and in general it is recommended that the maximum total dose does not exceed 300 mg. For continuous epidural or caudal anesthesia, the maximum recommended dosage should not be administered at intervals of less than 90 minutes. When continuous lumbar or caudal epidural anesthesia is used for non-obstetrical procedures, more drug may be administered if required to produce adequate anesthesia.

The maximum recommended dose per 90 minute period of lidocaine hydrochloride for paracervical block in obstetrical patients and non-obstetrical patients is 200 mg total. One-half of the total dose is usually administered to each side. Inject slowly five minutes between sides. (See also discussion of paracervical block in PRECAUTIONS).

For intravenous regional anesthesia, the dose administered should not exceed 4 mg/kg in adults.

Children: It is difficult to recommend a maximum dose of any drug for children, since this varies as a function of age and weight. For children over 3 years of age who have a normal lean body mass and normal body development, the maximum dose is determined by the child’s age and weight. For example, in a child of 5 years weighing 50 lbs., the dose of lidocaine HCl should not exceed 75 — 100 mg (1.5
— 2 mg/lb). The use of even more dilute solutions (i.e., 0.25 — 0.5%) and total dosages not to exceed 3 mg/kg (1.4 mg/lb) are recommended for induction of intravenous regional anesthesia in children.

In order to guard against systemic toxicity, the lowest effective concentration and lowest effective dose should be used at all times. In some cases it will be necessary to dilute available concentrations with 0.9% sodium chloride injection in order to obtain the required final concentration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. Solutions that are discolored and/or contain particulate matter should not be used.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Lidocaine Hydrochloride Injection, USP (without Epinephrine)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conc. (%)</td>
</tr>
<tr>
<td>Infiltration</td>
<td></td>
</tr>
<tr>
<td>Percutaneous</td>
<td>0.5 or 1.0</td>
</tr>
<tr>
<td>Intravenous Regional</td>
<td>0.5</td>
</tr>
<tr>
<td>Peripheral Nerve Blocks, e.g.</td>
<td></td>
</tr>
<tr>
<td>Brachial</td>
<td>1.5</td>
</tr>
<tr>
<td>Dental</td>
<td>2.0</td>
</tr>
<tr>
<td>Intercostal</td>
<td>1.0</td>
</tr>
<tr>
<td>Paravertebral</td>
<td>1.0</td>
</tr>
<tr>
<td>Pudendal (each side)</td>
<td>1.0</td>
</tr>
<tr>
<td>Paracervical</td>
<td></td>
</tr>
<tr>
<td>Obstetrical Analgesia (each side)</td>
<td>1.0</td>
</tr>
<tr>
<td>Sympathetic Nerve Blocks, e.g.</td>
<td></td>
</tr>
<tr>
<td>Cervical (stellate ganglion)</td>
<td>1.0</td>
</tr>
<tr>
<td>Lumbar</td>
<td>1.0</td>
</tr>
<tr>
<td>Central Neural Blocks</td>
<td></td>
</tr>
<tr>
<td>Epidural*</td>
<td></td>
</tr>
<tr>
<td>Thoracic</td>
<td>1.0</td>
</tr>
<tr>
<td>Lumbar</td>
<td>1.0</td>
</tr>
<tr>
<td>Analgesia</td>
<td>1.0</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>1.5</td>
</tr>
<tr>
<td>Caudal</td>
<td>2.0</td>
</tr>
<tr>
<td>Obstetrical Analgesia</td>
<td>1.0</td>
</tr>
<tr>
<td>Surgical Anesthesia</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*Dose determined by number of dermatomes to be anesthetized (2 to 3 mL/dermatome).
THE ABOVE SUGGESTED CONCENTRATIONS AND VOLUMES SERVE ONLY AS A GUIDE. OTHER VOLUMES AND CONCENTRATIONS MAY BE USED PROVIDED THE TOTAL MAXIMUM RECOMMENDED DOSE IS NOT EXCEEDED.

Sterilization, Storage and Technical Procedures: Disinfecting agents containing heavy metals, which cause release of respective ions (mercury, zinc, copper, etc.) should not be used for skin or mucous membrane disinfection as they have been related to incidence of swelling and edema. When chemical disinfection of multi-dose vials is desired, either isopropyl alcohol (91%) or 70% ethyl alcohol is recommended. Many commercially available brands of rubbing alcohol, as well as solutions of ethyl alcohol not of USP grade, contain denaturants which are injurious to rubber and, therefore, are not to be used. 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.

HOW SUPPLIED

Lidocaine Hydrochloride Injection, USP is supplied as follows:

<table>
<thead>
<tr>
<th>NDC</th>
<th>Container</th>
<th>Concentration</th>
<th>Size</th>
<th>Total (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-dose:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0409-4278-01 Glass Teartop Vial</td>
<td>0.5% (5 mg/mL)</td>
<td>50 mL</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>0409-4713-01 Glass Ampul</td>
<td>1% (10 mg/mL)</td>
<td>2 mL (bulk – 400 units)</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>0409-4713-02 Glass Ampul</td>
<td>1% (10 mg/mL)</td>
<td>5 mL</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>0409-4713-03 Glass Ampul</td>
<td>1% (10 mg/mL)</td>
<td>5 mL (bulk – 400 units)</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>0409-4713-20 Glass Ampul</td>
<td>1% (10 mg/mL)</td>
<td>20 mL</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>0409-4713-32 Glass Ampul</td>
<td>1% (10 mg/mL)</td>
<td>2 mL</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>0409-4713-62 Glass Ampul</td>
<td>1% (10 mg/mL)</td>
<td>2 mL (bulk – 800 units)</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>0409-4713-65 Glass Ampul</td>
<td>1% (10 mg/mL)</td>
<td>5 mL (bulk – 800 units)</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>0409-4279-02 Glass Teartop Vial</td>
<td>1% (10 mg/mL)</td>
<td>30 mL</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>0409-4270-01 Sterile Glass Teartop Vial</td>
<td>1% (10 mg/mL)</td>
<td>30 mL</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>0409-4776-01 Glass Ampul</td>
<td>1.5% (15 mg/mL)</td>
<td>20 mL</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>0409-4056-01 Sterile Glass Ampul</td>
<td>1.5% (15 mg/mL)</td>
<td>20 mL</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>0409-4282-01 Glass Ampul</td>
<td>2% (20 mg/mL)</td>
<td>2 mL</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>0409-4282-02 Glass Ampul</td>
<td>2% (20 mg/mL)</td>
<td>10 mL</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Multiple-dose:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0409-4275-01 Plastic Fliptop Vial</td>
<td>0.5% (5 mg/mL)</td>
<td>50 mL</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>0409-4276-01 Plastic Fliptop Vial</td>
<td>1% (10 mg/mL)</td>
<td>20 mL</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>0409-4276-02 Plastic Fliptop Vial</td>
<td>1% (10 mg/mL)</td>
<td>50 mL</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>0409-4277-01 Plastic Fliptop Vial</td>
<td>2% (20 mg/mL)</td>
<td>20 mL</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>0409-4277-02 Plastic Fliptop Vial</td>
<td>2% (20 mg/mL)</td>
<td>50 mL</td>
<td>1000</td>
<td></td>
</tr>
</tbody>
</table>

Single-dose products are preservative-free.

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

Lidocaine Hydrochloride Injection, USP solutions packaged in ampuls and glass teartop vials may be autoclaved one time only. Autoclave at 15 pounds pressure, 121°C (250°F) for 15 minutes. DO NOT AUTOCLAVE PRODUCT IN PLASTIC VIALS.

Revised: February, 2010

Printed in USA EN-2421

Hospira, Inc., Lake Forest, IL 60045 USA
EXP 1 SEP 2013
LOT 931153A

RL-1467 (9/05)

5 mL
NDC 0409-4713-65

Preservative-Free

1% LIDOCAINE HCl
Injection, USP
10 mg/mL

Rx only

HOSPIRA, INC.
LAKE FOREST, IL 60045 USA
BUPIVACAINE (bupivacaine hydrochloride) injection, solution
[Hospira, Inc.]
Bupivacaine HCl 0.75% in Dextrose
8.25% Injection
Sterile Hyperbaric Solution for
Spinal Anesthesia
Rx only
DESCRIPTION
Bupivacaine hydrochloride is 1-Butyl-2′ 6′-pipecoloxylidide monochloride, monohydrate, a white crystalline powder that is freely soluble in 95 percent ethanol, soluble in water, and slightly soluble in chloroform or acetone. It has the following structural formula:

CH₃CH₂CH₂CH₂CH₂
\begin{align*}
N & \quad \text{CONH} \\
\end{align*}
\begin{align*}
\text{CH₃} & \quad \text{HCl} \\
\text{CH₃} & \quad \text{H₂O}
\end{align*}

Dextrose is D-glucopyranose monohydrate and has the following structural formula:

D-glucopyranose monohydrate

Bupivacaine Spinal (Bupivacaine in Dextrose Injection, USP) is available in sterile, hyperbaric solution for subarachnoid injection (spinal block).

Bupivacaine hydrochloride is related chemically and pharmacologically to the aminoacyl local anesthetics. It is a homologue of mepivacaine and is chemically related to lidocaine. All three of these anesthetics contain an amide linkage between the aromatic nucleus and the amino or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage.

Each 1 mL of Bupivacaine Spinal contains 7.5 mg bupivacaine hydrochloride, anhydrous and 82.5 mg
dextrose, anhydrous. The pH of this solution is adjusted to 5.5 (4.0 to 6.5) with sodium hydroxide and/or hydrochloric acid.

The specific gravity of Bupivacaine Spinal is between 1.030 and 1.035 at 25°C and 1.03 at 37°C.

Bupivacaine Spinal does not contain any preservatives.

Solutions of bupivacaine hydrochloride may be autoclaved if they do not contain epinephrine.

**CLINICAL PHARMACOLOGY**

Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the 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.

Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous system (CNS). At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Recent clinical reports and animal research suggest that these cardiovascular changes are more likely to occur after unintended direct intravascular injection of bupivacaine. Therefore, when epidural anesthesia with bupivacaine is considered, incremental dosing is necessary.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression or both. Apparent central stimulation is manifested as restlessness, tremors and shivering, progressing to convulsions, followed by depression and coma progressing ultimately to 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.

Pharmacokinetics: The rate of systemic absorption of local anesthetics is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution. A dilute concentration of epinephrine (1:200,000 or 5 μg/mL) usually reduces the rate of absorption and peak plasma concentration of bupivacaine, permitting the use of moderately larger total doses and sometimes prolonging the duration of action.

The onset of action with bupivacaine is rapid and anesthesia is long-lasting. The duration of anesthesia is significantly longer with bupivacaine than with any other commonly used local anesthetic. It has also been noted that there is a period of analgesia that persists after the return of sensation, during which time the need for strong analgesics is reduced.

The onset of sensory blockade following spinal block with Bupivacaine Spinal (bupivacaine in dextrose injection, USP) is very rapid (within one minute), maximum motor blockade and maximum dermatome level are achieved within 15 minutes in most cases. Duration of sensory blockade (time to return of complete sensation in the operative site or regression of two dermatomes) following a 12 mg dose averages 2 hours with or without 0.2 mg epinephrine. The time to return of complete motor ability with 12 mg Bupivacaine Spinal (bupivacaine in dextrose injection, USP) averages 3½ hours without the addition of epinephrine and 4½ hours if 0.2 mg epinephrine is added. When compared to equal milligram doses of hyperbaric tetracaine, the duration of sensory blockade was the same but the time to complete motor recovery was significantly longer for tetracaine. Addition of 0.2 mg epinephrine significantly prolongs the motor blockade and time to first postoperative narcotic with Bupivacaine Spinal (bupivacaine in dextrose injection, USP).
Local anesthetics appear to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer. Bupivacaine with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, nonionized drugs readily enter the fetal blood from the maternal circulation.

Depending upon the route of administration, local anesthetics are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart and brain.

Pharmacokinetic studies on the plasma profiles of bupivacaine after direct intravenous injection suggest a three-compartment open model. The first compartment is represented by the rapid intravascular distribution of the drug. The second compartment represents the equilibration of the drug throughout the highly perfused organs such as the brain, myocardium, lungs, kidneys and liver. The third compartment represents an equilibration of the drug with poorly perfused tissues, such as muscle and fat. The elimination of drug from tissue distribution depends largely upon the ability of binding sites in the circulation to carry it to the liver where it is metabolized.

Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic or renal disease, addition of epinephrine, factors affecting urinary pH, renal blood flow, the route of drug administration, and the age of the patient. The half-life of bupivacaine in adults is $3.5 \pm 2$ hours and in neonates $8.1$ hours.

Amide-type local anesthetics such as bupivacaine are metabolized primarily in the liver via conjugation with glucuronic acid. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Pipecoloxylidine is the major metabolite of bupivacaine.

The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by renal perfusion and factors affecting urinary pH. Only 5% of bupivacaine is excreted unchanged in the urine.

When administered in recommended doses and concentrations, bupivacaine does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.

INDICATIONS AND USAGE

Bupivacaine Spinal is indicated for the production of subarachnoid block (spinal anesthesia).

Standard textbooks should be consulted to determine the accepted procedures and techniques for the administration of spinal anesthesia.

CONTRAINDICATIONS

Bupivacaine Spinal (Bupivacaine in Dextrose Injection, USP) is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type.

The following conditions preclude the use of spinal anesthesia:

Severe hemorrhage, severe hypotension or shock and arrhythmias, such as complete heart block, which severely restrict cardiac output.

Local infection at the site of proposed lumbar puncture.

Septicemia.

WARNINGS

LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER
ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING 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. (See also ADVERSE REACTIONS, PRECAUTIONS and OVERDOSAGE.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST, AND, POSSIBLY, DEATH.

Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of gleno-humeral chondrolysis have been described in pediatric and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. The time of onset of symptoms, such as joint pain, stiffness and loss of motion can be variable, but may begin as early as the 2nd month after surgery. Currently, there is no effective treatment for chondrolysis; patients who experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

Spinal anesthetics should not be injected during uterine contractions, because spinal fluid current may carry the drug further cephalad than desired.

A free flow of cerebrospinal fluid during the performance of spinal anesthesia is indicative of entry into the subarachnoid space. However, aspiration should be performed before the anesthetic solution is injected to confirm entry into the subarachnoid space and to avoid intravascular injection.

Bupivacaine solutions containing epinephrine or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because a severe persistent hypertension may occur. Likewise, solutions of bupivacaine containing a vasoconstrictor, such as epinephrine, should be used with extreme caution in patients receiving monoamine oxidase inhibitors (MAOIs) or antidepressants of the triptyline or imipramine types, because severe prolonged hypertension may result.

Until further experience is gained in patients younger than 18 years, administration of bupivacaine in this age group is not recommended.

Mixing or the prior or intercurrent use of any other local anesthetic with bupivacaine cannot be recommended because of insufficient data on the clinical use of such mixtures.

PRECAUTIONS

General: The safety and effectiveness of spinal anesthetics depend on proper dosage, correct technique, adequate precautions and readiness for emergencies. Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use. (See WARNINGS, ADVERSE REACTIONS and OVERDOSAGE.) The patient should have I.V. fluids running via an indwelling catheter to assure a functioning intravenous pathway. The lowest dosage of local anesthetic that results in effective anesthesia should be used. Aspiration for blood should be performed before injection and injection should be made slowly. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients may require reduced doses. Reduced doses may also be indicated in patients with increased intra-abdominal pressure (including obstetrical patients), if otherwise suitable for spinal anesthesia.

There should be careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness after local anesthetic injection. Restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity.
Spinal anesthetics should be used with caution in patients with severe disturbances of cardiac rhythm, shock, or heart block.

Sympathetic blockade occurring during spinal anesthesia may result in peripheral vasodilation and hypotension, the extent depending on the number of dermatomes blocked. Blood pressure should, therefore, be carefully monitored especially in the early phases of anesthesia. Hypotension may be controlled by vasoconstrictors in dosages depending on the severity of hypotension and response of treatment. The level of anesthesia should be carefully monitored because it is not always controllable in spinal techniques.

Because amide-type local anesthetics such as bupivacaine are metabolized by the liver, 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 of developing toxic plasma concentrations. Local anesthetics should also be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by these drugs. However, dosage recommendations for spinal anesthesia are much lower than dosage recommendations for other major blocks and most experience regarding hepatic and cardiovascular disease dose-related toxicity is derived from these other major blocks.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of potent inhalation agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Because it is not known whether amide-type local anesthetics may trigger this reaction and because the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and prompt institution of treatment, including oxygen therapy, indicated supportive measures, and dantrolene. (Consult dantrolene sodium intravenous package insert before using.)

The following conditions may preclude the use of spinal anesthesia, depending upon the physician’s evaluation of the situation and ability to deal with the complications or complaints which may occur:

- Pre-existing diseases of the central nervous system, such as those attributable to pernicious anemia, poliomyelitis, syphilis, or tumor.
- Hematological disorders predisposing to coagulopathies or patients on anticoagulant therapy. Trauma to a blood vessel during the conduct of spinal anesthesia may, in some instances, result in uncontrollable central nervous system hemorrhage or soft tissue hemorrhage.
- Chronic backache and preoperative headache.
- Hypotension and hypertension.
- Technical problems (persistent paresthesias, persistent bloody tap).
- Arthritis or spinal deformity.
- Extremes of age.
- Psychosis or other causes of poor cooperation by the patient.

Information for Patients: When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body, following proper administration of spinal anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the Bupivacaine Spinal (Bupivacaine in
Clinically Significant Drug Interactions: The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs and of ergot-type oxytocic drugs may cause severe persistent hypertension or cerebrovascular accidents.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals to evaluate the carcinogenic potential of bupivacaine hydrochloride have not been conducted. The mutagenic potential and the effect on fertility of bupivacaine hydrochloride have not been determined.

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Bupivacaine Spinal should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Bupivacaine hydrochloride produced developmental toxicity when administered subcutaneously to pregnant rats and rabbits at clinically relevant doses. This does not exclude the use of Bupivacaine Spinal at term for obstetrical anesthesia or analgesia. (See Labor and Delivery.)

Bupivacaine hydrochloride was administered subcutaneously to rats at doses of 4.4, 13.3, & 40 mg/kg and to rabbits at doses of 1.3, 5.8, & 22.2 mg/kg during the period of organogenesis (implantation to closure of the hard palate). The high doses are approximately 30-times the daily maximum recommended human dose (MRHD) of 12 mg/day on a mg dose/m² body surface area (BSA) basis. No embryo-fetal effects were observed in rats at the high dose which caused increased maternal lethality. An increase in embryo-fetal deaths was observed in rabbits at the high dose in the absence of maternal toxicity with the fetal No Observed Adverse Effect Level being approximately 8-times the MRHD on a BSA basis.

In a rat pre- and post-natal development study (dosing from implantation through weaning) conducted at subcutaneous doses of 4.4, 13.3, & 40 mg/kg, decreased pup survival was observed at the high dose. The high dose is approximately 30-times the daily MRHD of 12 mg/day on a BSA basis.

Labor and Delivery: Spinal anesthesia has a recognized use during labor and delivery. Bupivacaine hydrochloride, when administered properly, via the epidural route in doses 10 to 12 times the amount used in spinal anesthesia has been used for obstetrical analgesia and anesthesia without evidence of adverse effects on the fetus.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient’s legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously and electronic fetal monitoring is highly advisable.

It is extremely important to avoid aortocaval compression by the gravid uterus during administration of regional block to parturients. To do this, the patient must be maintained in the left lateral decubitus position or a blanket roll or sandbag may be placed beneath the right hip and the gravid uterus displaced to the left.

Spinal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Spinal anesthesia has also been reported to prolong the second stage of labor by removing the parturient’s reflex urge to bear down or by interfering with motor function. The use of obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may be followed by diminished muscle strength and tone for the first day or two of life. This has not been reported with bupivacaine.
There have been reports of cardiac arrest during use of bupivacaine hydrochloride 0.75% solution for epidural anesthesia in obstetrical patients. The package insert for bupivacaine hydrochloride for epidural, nerve block, etc. has a more complete discussion of preparation for, and management of, this problem. These cases are compatible with systemic toxicity following unintended intravascular injection of the much larger dose recommended for epidural anesthesia and have not occurred within the dose range of bupivacaine hydrochloride 0.75% recommended for spinal anesthesia in obstetrics. The 0.75% concentration of bupivacaine hydrochloride is therefore not recommended for obstetrical epidural anesthesia. Bupivacaine Spinal (bupivacaine in dextrose injection, USP) is recommended for spinal anesthesia in obstetrics.

Nursing Mothers: It is not known whether local anesthetic drugs are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when local anesthetic drugs are administered to a nursing woman.

Pediatric Use: Until further experience is gained in patients younger than 18 years, administration of Bupivacaine Spinal in this age group is not recommended.

ADVERSE REACTIONS

Reactions to bupivacaine are characteristic of those associated with other amide-type local anesthetics. The most commonly encountered acute adverse experiences which demand immediate countermeasures following the administration of spinal anesthesia are hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia. These may lead to cardiac arrest if untreated. In addition, dose-related convulsions and cardiovascular collapse may result from diminished tolerance, rapid absorption from the injection site or from unintentional intravascular injection of a local anesthetic solution. Factors influencing plasma protein binding, such as acidosis, systemic diseases which alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance.

Respiratory System: Respiratory paralysis or underventilation may be noted as a result of upward extension of the level of spinal anesthesia and may lead to secondary hypoxic cardiac arrest if untreated. Preanesthetic medication, intraoperative analgesics and sedatives, as well as surgical manipulation, may contribute to underventilation. This will usually be noted within minutes of the injection of spinal anesthetic solution, but because of differing surgical maximal onset times, differing intercurrent drug usage and differing manipulation, it may occur at any time during surgery or the immediate recovery period.

Cardiovascular System: Hypotension due to loss of sympathetic tone is a commonly encountered extension of the clinical pharmacology of spinal anesthesia. This is more commonly observed in patients with shrunken blood volume, shrunken interstitial fluid volume, cephalad spread of the local anesthetic, and/or mechanical obstruction of venous return. Nausea and vomiting are frequently associated with hypotensive episodes following the administration of spinal anesthesia. High doses, or inadvertent intravascular injection, may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, bradycardia, heart block, ventricular arrhythmias, and, possibly, cardiac arrest. (See WARNINGS, PRECAUTIONS, and OVERDOSAGE sections.)

Central Nervous System: Respiratory paralysis or underventilation secondary to cephalad spread of the level of spinal anesthesia (see Respiratory System) and hypotension for the same reason (see Cardiovascular System) are the two most commonly encountered central nervous system-related adverse observations which demand immediate countermeasures.

High doses or inadvertent intravascular injection may lead to high plasma levels and related central nervous system toxicity characterized by excitement and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest.
Neurologic: The incidences of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local 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 a contribution from the drug.

Neurologic effects following spinal anesthesia may include loss of perineal sensation and sexual function, persistent anesthetia, paresthesia, weakness and paralysis of the lower extremities, and loss of sphincter control all of which may have slow, incomplete, or no recovery, hypotension, high or total spinal block, urinary retention, headache, backache, septic meningitis, meningismus, arachnoiditis, slowing of labor, increased incidence of forceps delivery, shivering, cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid, and fecal and urinary incontinence.

Allergic: 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, pruritus, 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 has been reported. The usefulness of screening for sensitivity has not been definitely established.

Other: Nausea and vomiting may occur during spinal anesthesia.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use or to underventilation (and perhaps apnea) secondary to upward extension of spinal anesthesia. Hypotension is commonly encountered during the conduct of spinal anesthesia due to relaxation of sympathetic tone, and sometimes, contributory mechanical obstruction of venous return.

Management of Local Anesthetic Emergencies: The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient’s state of consciousness after each local anesthetic injection. 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 a high or total spinal, 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 the convulsions. A 50 mg to 100 mg bolus I.V. injection of succinylcholine will paralyze the patient without depressing the central nervous or cardiovascular systems and facilitate ventilation. A bolus I.V. dose of 5 mg to 10 mg of diazepam or 50 mg to 100 mg of thiopental will permit ventilation and counteract central nervous system stimulation, but these drugs also depress central nervous system, respiratory and cardiac function, add to postictal depression and may result in apnea. Intravenous barbiturates, anticonvulsant 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).

Hypotension due to sympathetic relaxation may be managed by giving intravenous fluids (such as Sodium Chloride Injection 0.9% or Lactated Ringer’s Injection), in an attempt to relieve mechanical obstruction of venous return, or by using vasopressors (such as ephedrine which increases the force of myocardial contractions) and, if indicated, by giving plasma expanders or whole blood.

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

Recent clinical data from patients experiencing local anesthetic-induced convulsions demonstrated rapid development of hypoxia, hypercarbia, and acidosis with bupivacaine within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

If not treated immediately, convulsions with simultaneous hypoxia, hypercarbia and acidosis plus myocardial depression from the direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities, including apnea, may occur. Underventilation or apnea due to a high or total spinal may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted and maintained for a prolonged period if necessary. Recovery has been reported after prolonged resuscitative efforts.

The supine position is dangerous in pregnant women at term because of aortocaval 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 be accomplished.

The mean seizure dosage of bupivacaine in rhesus monkeys was found to be 4.4 mg/kg with mean arterial plasma concentration of 4.5 µg/mL. The intravenous and subcutaneous LD50 in mice is 6 mg/kg to 8 mg/kg and 38 mg/kg to 54 mg/kg, respectively.

**DOSAGE AND ADMINISTRATION**

The dose of any local anesthetic administered varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. The smallest dose and concentration required to produce the desired result should be administered. Dosages of Bupivacaine Spinal (Bupivacaine in Dextrose Injection, USP) should be reduced for elderly and debilitated patients and patients with cardiac and/or liver disease.

For specific techniques and procedures, refer to standard textbooks.

There have been adverse event reports of chondrolysis in patients receiving intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures. Bupivacaine Spinal is not approved for this use (see WARNINGS and DOSAGE AND ADMINISTRATION).

The extent and degree of spinal anesthesia depends upon several factors including dosage, specific gravity of the anesthetic solution, volume of solution used, force of injection, level of puncture, and position of the patient during and immediately after injection.

Seven and one-half mg (7.5 mg or 1.0 mL) Bupivacaine Spinal has generally proven satisfactory for spinal anesthesia for lower extremity and perineal procedures including TURP and vaginal hysterectomy. Twelve mg (12 mg or 1.6 mL) has been used for lower abdominal procedures such as abdominal hysterectomy, tubal ligation, and appendectomy. These doses are recommended as a guide for use in the average adult and may be reduced for elderly or debilitated patients. Because experience with Bupivacaine Spinal is limited in patients below the age of 18 years, dosage recommendations in this age group cannot be made.

Obstetrical Use: Doses as low as 6 mg bupivacaine hydrochloride have been used for vaginal delivery under spinal anesthesia. The dose range of 7.5 mg to 10.5 mg (1 mL to 1.4 mL) bupivacaine hydrochloride has been used for Cesarean section under spinal anesthesia.

In recommended doses, Bupivacaine Spinal produces complete motor and sensory block.
Unused portions of solutions should be discarded following initial use.

Bupivacaine Spinal should be inspected visually for discoloration and particulate matter prior to administration; solutions which are discolored or which contain particulate matter should not be administered.

Bupivacaine Spinal may be autoclaved once at 15 pounds pressure, 121°C (250°F) for 15 minutes. Do not administer any solution which is discolored or contains particulate matter.

HOW SUPPLIED

Bupivacaine Spinal (Bupivacaine in Dextrose Injection, USP) is supplied in 2 mL ampuls (15 mg bupivacaine hydrochloride with 165 mg dextrose anhydrous) packaged in cartons of 10 (NDC No. 0409-3613-01).

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

Revised: 01/2013

EN-3185

Hospira, Inc., Lake Forest, IL 60045 USA

Package Label Display Panel
Description

Bupivacaine Hydrochloride is 2-Piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate, a white crystalline powder that is freely soluble in 95 percent ethanol, soluble in water, and slightly soluble in chloroform or acetone. It has the following structural formula:
Epinephrine is (-)-3,4-Dihydroxy-α-[methylamino)methyl] benzyl alcohol. It has the following structural formula:

Bupivacaine Hydrochloride is available in sterile isotonic solutions with and without epinephrine (as bitartrate) 1:200,000 for injection via local infiltration, peripheral nerve block, and caudal and lumbar epidural blocks. Solutions of Bupivacaine Hydrochloride may be autoclaved if they do not contain epinephrine. Solutions are clear and colorless.

Bupivacaine is related chemically and pharmacologically to the aminoacyl local anesthetics. It is a homologue of mepivacaine and is chemically related to lidocaine. All three of these anesthetics contain an amide linkage between the aromatic nucleus and the amino, or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage.

Bupivacaine Hydrochloride Injection, USP is available in sterile, isotonic solutions containing bupivacaine hydrochloride in water for injection with characteristics as follows:

**Bupivacaine Hydrochloride Injection, USP (without epinephrine)**

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Bupivacaine Hydrochloride mg/mL</th>
<th>Sodium Chloride mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25%</td>
<td>2.5</td>
<td>8.6</td>
</tr>
<tr>
<td>0.5%</td>
<td>5</td>
<td>8.1</td>
</tr>
<tr>
<td>0.75%</td>
<td>7.5</td>
<td>7.6</td>
</tr>
</tbody>
</table>

May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. (See HOW SUPPLIED section for pH information.) Multiple-dose vials contain methylparaben 1 mg/mL added as a preservative.

Bupivacaine and Epinephrine Injection, USP is available in sterile, isotonic solutions containing bupivacaine hydrochloride and epinephrine 1:200,000 with characteristics as follows:

**Bupivacaine and Epinephrine Injection, USP**

<table>
<thead>
<tr>
<th>Concentration (Bupivacaine HCl)</th>
<th>Bupivacaine Hydrochloride mg/mL</th>
<th>Epinephrine 1:200,000 mcg/mL</th>
<th>Sodium Chloride mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25%</td>
<td>2.5</td>
<td>5</td>
<td>8.5</td>
</tr>
<tr>
<td>0.5%</td>
<td>5</td>
<td>5</td>
<td>8.5</td>
</tr>
<tr>
<td>0.75%</td>
<td>7.5</td>
<td>5</td>
<td>8.5</td>
</tr>
</tbody>
</table>
Sodium metabisulfite 0.1 mg/mL added as antioxidant and edetate calcium disodium, anhydrous 0.1 mg/mL added as stabilizer. May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. (See HOW SUPPLIED section for pH information.) Multiple-dose vials contain methylparaben 1 mg/mL added as a preservative.

Single-dose solutions contain no added bacteriostat or anti-microbial agent and unused portions should be discarded after use.

CLINICAL PHARMACOLOGY

Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the 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.

Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems (CNS). At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Recent clinical reports and animal research suggest that these cardiovascular changes are more likely to occur after unintended intravascular injection of bupivacaine. Therefore, incremental dosing is necessary.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central stimulation is manifested as restlessness, tremors and shivering progressing to convulsions, followed by depression and coma progressing ultimately to 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 state.

Pharmacokinetics: The rate of systemic absorption of local anesthetics is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution. A dilute concentration of epinephrine (1:200,000 or 5 mcg/mL) usually reduces the rate of absorption and peak plasma concentration of Bupivacaine Hydrochloride, permitting the use of moderately larger total doses and sometimes prolonging the duration of action.

The onset of action with Bupivacaine Hydrochloride is rapid and anesthesia is long lasting. The duration of anesthesia is significantly longer with Bupivacaine Hydrochloride than with any other commonly used local anesthetic. It has also been noted that there is a period of analgesia that persists after the return of sensation, during which time the need for strong analgesics is reduced.

Local anesthetics are bound to plasma proteins in varying degrees. Generally, the lower the plasma concentration of drug the higher the percentage of drug bound to plasma proteins.

Local anesthetics appear to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer. Bupivacaine Hydrochloride with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, nonionized drugs readily enter the fetal blood from the maternal circulation.

Depending upon the route of administration, local anesthetics are distributed to some extent to all body
tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain.

Pharmacokinetic studies on the plasma profile of Bupivacaine Hydrochloride after direct intravenous injection suggest a three-compartment open model. The first compartment is represented by the rapid intravascular distribution of the drug. The second compartment represents the equilibration of the drug throughout the highly perfused organs such as the brain, myocardium, lungs, kidneys, and liver. The third compartment represents an equilibration of the drug with poorly perfused tissues, such as muscle and fat. The elimination of drug from tissue distribution depends largely upon the ability of binding sites in the circulation to carry it to the liver where it is metabolized.

After injection of Bupivacaine Hydrochloride for caudal, epidural, or peripheral nerve block in man, peak levels of bupivacaine in the blood are reached in 30 to 45 minutes, followed by a decline to insignificant levels during the next three to six hours.

Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic or renal disease, addition of epinephrine, factors affecting urinary pH, renal blood flow, the route of drug administration, and the age of the patient. The half-life of Bupivacaine Hydrochloride in adults is 2.7 hours and in neonates 8.1 hours.

In clinical studies, elderly patients reached the maximal spread of analgesia and maximal motor blockade more rapidly than younger patients. Elderly patients also exhibited higher peak plasma concentrations following administration of this product. The total plasma clearance was decreased in these patients.

Amide-type local anesthetics such as Bupivacaine Hydrochloride are metabolized primarily in the liver via conjugation with glucuronic acid. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Pipexoloxylidine is the major metabolite of Bupivacaine Hydrochloride.

The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Only 6% of bupivacaine is excreted unchanged in the urine.

When administered in recommended doses and concentrations, Bupivacaine Hydrochloride does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.

INDICATIONS AND USAGE

Bupivacaine Hydrochloride is indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures. Only the 0.25% and 0.5% concentrations are indicated for obstetrical anesthesia. (See WARNINGS.)

Experience with nonobstetrical surgical procedures in pregnant patients is not sufficient to recommend use of 0.75% concentration of Bupivacaine Hydrochloride in these patients.

Bupivacaine Hydrochloride is not recommended for intravenous regional anesthesia (Bier Block). (See WARNINGS.)

The routes of administration and indicated Bupivacaine Hydrochloride concentrations are:

- local infiltration 0.25%
- peripheral nerve block 0.25% and 0.5%
- retrobulbar block 0.75%
- sympathetic block 0.25%
- lumbar epidural 0.25%, 0.5%, and 0.75%
- (0.75% not for obstetrical anesthesia)
- caudal 0.25% and 0.5%
- epidural test dose 0.5% with epinephrine 1:200,000

(See DOSAGE AND ADMINISTRATION for additional information.)

Standard textbooks should be consulted to determine the accepted procedures and techniques for the administration of Bupivacaine Hydrochloride.

CONTRAINDICATIONS
Bupivacaine Hydrochloride is contraindicated in obstetrical paracervical block anesthesia. Its use in this technique has resulted in fetal bradycardia and death.

Bupivacaine Hydrochloride is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type or to other components of Bupivacaine Hydrochloride solutions.

WARNINGS

THE 0.75% CONCENTRATION OF BUPIVACAINE HYDROCHLORIDE IS NOT RECOMMENDED FOR OBSTETRICAL ANESTHESIA. THERE HAVE BEEN REPORTS OF CARDIAC ARREST WITH DIFFICULT RESUSCITATION OR DEATH DURING USE OF BUPIVACAINE HYDROCHLORIDE FOR EPIDURAL ANESTHESIA IN OBSTETRICAL PATIENTS. IN MOST CASES, THIS HAS FOLLOWED USE OF THE 0.75% CONCENTRATION. RESUSCITATION HAS BEEN DIFFICULT OR IMPOSSIBLE DESPITE APPARENTLY ADEQUATE PREPARATION AND APPROPRIATE MANAGEMENT. CARDIAC ARREST HAS OCCURRED AFTER CONVULSIONS RESULTING FROM SYSTEMIC TOXICITY, PRESUMABLY FOLLOWING UNINTENTIONAL INTRAVASCULAR INJECTION. THE 0.75% CONCENTRATION SHOULD BE RESERVED FOR SURGICAL PROCEDURES WHERE A HIGH DEGREE OF MUSCLE RELAXATION AND PROLONGED EFFECT ARE NECESSARY.

LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING 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. (See also ADVERSE REACTIONS, PRECAUTIONS, and OVERDOSAGE.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE, AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

Local anesthetic solutions containing antimicrobial preservatives, i.e., those supplied in multiple-dose vials, should not be used for epidural or caudal anesthesia because safety has not been established with regard to intrathecal injection, either intentionally or unintentionally, of such preservatives.

Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of gleno-humeral chondrolysis have been described in pediatric and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. The time of onset of symptoms, such as joint pain, stiffness and loss of motion can be variable, but may begin as early as the 2nd month after surgery. Currently, there is no effective treatment for chondrolysis; patients who experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

It is essential that aspiration for blood or cerebrospinal fluid (where applicable) be done prior to injecting any local anesthetic, both the original dose and all subsequent doses, to avoid intravascular or subarachnoid injection. However, a negative aspiration does not ensure against an intravascular or subarachnoid injection.

Bupivacaine Hydrochloride with epinephrine 1:200,000 or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because a severe persistent hypertension may occur. Likewise, solutions of Bupivacaine Hydrochloride containing a vasoconstrictor, such as epinephrine, should be used with extreme caution in patients receiving monoamineoxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe prolonged hypertension may result.
Until further experience is gained in pediatric patients younger than 12 years, administration of Bupivacaine Hydrochloride in this age group is not recommended.

Mixing or the prior or intercurrent use of any other local anesthetic with Bupivacaine Hydrochloride cannot be recommended because of insufficient data on the clinical use of such mixtures. There have been reports of cardiac arrest and death during the use of Bupivacaine Hydrochloride for intravenous regional anesthesia (Bier Block). Information on safe dosages and techniques of administration of Bupivacaine Hydrochloride in this procedure is lacking. Therefore, Bupivacaine Hydrochloride is not recommended for use in this technique.

Bupivacaine Hydrochloride with epinephrine 1:200,000 contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people. Single-dose ampuls and single-dose vials of Bupivacaine Hydrochloride without epinephrine do not contain sodium metabisulfite.

PRECAUTIONS

General: The safety and effectiveness of local anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. (See WARNINGS, ADVERSE REACTIONS, and OVERDOSAGE.) During major regional nerve blocks, the patient should have IV fluids running via an indwelling catheter to assure a functioning intravenous pathway. The lowest dosage of local anesthetic that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should be used when feasible.

Epidural Anesthesia: During epidural administration of Bupivacaine Hydrochloride, 0.5% and 0.75% solutions should be administered in incremental doses of 3 mL to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Injections should be made slowly, with frequent aspirations before and during the injection to avoid intravascular injection. Syringe aspirations should also be performed before and during each supplemental injection in continuous (intermittent) 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 be administered initially and the effects monitored before the full dose is given. When using a “continuous” catheter technique, test doses should be given prior to both the original and all reinforcing doses, because plastic tubing in the epidural space can migrate into a blood vessel or through the dura. When clinical conditions permit, the test dose should contain epinephrine (10 mcg to 15 mcg has been suggested) to serve as a warning of unintended intravascular injection. If injected into a blood vessel, this amount of epinephrine is likely to produce a transient “epinephrine response” within 45 seconds, consisting of an increase in heart rate and/or systolic blood pressure, circumoral pallor, palpitations, and nervousness in the unsedated patient. The sedated patient may exhibit only a pulse rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, the heart rate should be monitored for a heart rate increase. Patients on beta-blockers may not manifest changes in heart rate, but blood pressure monitoring can detect a transient rise in systolic blood pressure. The test dose should also contain 10 mg to 15 mg of Bupivacaine Hydrochloride or an equivalent amount of another local anesthetic to detect an unintended intrathecal administration. This will be evidenced within a few minutes by signs of spinal block (e.g., decreased sensation of the buttocks, paresis of the legs, or, in the sedated patient, absent knee jerk). The Test Dose formulation of Bupivacaine Hydrochloride contains 15 mg of bupivacaine and 15 mcg of epinephrine in a volume of 3 mL. An intravascular or subarachnoid injection is still possible even if results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, high spinal or epinephrine-induced cardiovascular effects.

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 status of the patient. Debilitated, elderly
patients and acutely ill patients should be given reduced doses commensurate with their age and
physical status. Local anesthetics should also be used with caution in patients with hypotension or
heartblock.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs
and the patient’s state of consciousness should be performed after each local anesthetic injection. It
should be kept in mind at such times 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.

Local anesthetic solutions containing a vasoconstrictor should be used cautiously and in carefully
restricted quantities in areas of the body supplied by end arteries or having otherwise compromised
blood supply such as digits, nose, external ear, or penis. Patients with hypertensive vascular disease
may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result.

Because amide-local anesthetics such as Bupivacaine Hydrochloride are metabolized by the liver,
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 of developing toxic plasma concentrations. Local anesthetics should also be used with
cautions in patients with impaired cardiovascular function because they may be less able to compensate
for functional changes associated with the prolongation of AV conduction produced by these drugs.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such
as epinephrine are employed in patients during or following the administration of potent inhalation
anesthetics. In deciding whether to use these products concurrently in the same patient, the combined
action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and
the time since injection, when applicable, should be taken into account.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for
familial malignant hyperthermia. Because it is not known whether amide-type local anesthetics may
trigger this reaction and because the need for supplemental general anesthesia cannot be predicted in
advance, it is suggested that a standard protocol for management should be available. Early unexplained
signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature
elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect
triggering agent(s) and prompt institution of treatment, including oxygen therapy, indicated supportive
measures and dantrolene. (Consult dantrolene sodium intravenous package insert before using.)

Use in Head and Neck Area: Small doses of local anesthetics injected into the head and neck area,
including retrobulbar, dental, and stellate ganglion blocks, 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
intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. They may
also be due to puncture of the dural sheath of the optic nerve during retrobulbar block with diffusion of
any local anesthetic along the subdural space to the midbrain. Patients receiving these blocks should
have their circulation and respiration 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.)

Use in Ophthalmic Surgery: Clinicians who perform retrobulbar blocks should be aware that there have
been reports of respiratory arrest following local anesthetic injection. Prior to retrobulbar block, as
with all other regional procedures, the immediate availability of equipment, drugs, and personnel to
manage respiratory arrest or depression, convulsions, and cardiac stimulation or depression should be
assured (see also WARNINGS and Use In Head and Neck Area, above). As with other anesthetic
procedures, patients should be constantly monitored following ophthalmic blocks for signs of these
adverse reactions, which may occur following relatively low total doses.

A concentration of 0.75% bupivacaine is indicated for retrobulbar block; however, this concentration is not indicated for any other peripheral nerve block, including the facial nerve, and not indicated for local infiltration, including the conjunctiva (see INDICATIONS AND USAGE and PRECAUTIONS, General). Mixing Bupivacaine Hydrochloride with other local anesthetics is not recommended because of insufficient data on the clinical use of such mixtures.

When Bupivacaine Hydrochloride 0.75% is used for retrobulbar block, complete corneal anesthesia usually precedes onset of clinically acceptable external ocular muscle akinesia. Therefore, presence of akinesia rather than anesthesia alone should determine readiness of the patient for surgery.

Information for Patients: When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body, following proper administration of caudal or epidural anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the package insert of Bupivacaine Hydrochloride.

Clinically Significant Drug Interactions: The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs and of ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accidents.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate the carcinogenic potential of bupivacaine hydrochloride have not been conducted. The mutagenic potential and the effect on fertility of bupivacaine hydrochloride have not been determined.

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Bupivacaine Hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Bupivacaine hydrochloride produced developmental toxicity when administered subcutaneously to pregnant rats and rabbits at clinically relevant doses. This does not exclude the use of Bupivacaine at term for obstetrical anesthesia or analgesia. (See Labor and Delivery)

Bupivacaine hydrochloride was administered subcutaneously to rats at doses of 4.4, 13.3, & 40 mg/kg and to rabbits at doses of 1.3, 5.8, & 22.2 mg/kg during the period of organogenesis (implantation to closure of the hard palate). The high doses are comparable to the daily maximum recommended human dose (MRHD) of 400 mg/day on a mg/m2 body surface area (BSA) basis. No embryo-fetal effects were observed in rats at the high dose which caused increased maternal lethality. An increase in embryo-fetal deaths was observed in rabbits at the high dose in the absence of maternal toxicity with the fetal No Observed Adverse Effect Level representing approximately 1/5th the MRHD on a BSA basis.

In a rat pre- and post-natal development study (dosing from implantation through weaning) conducted at subcutaneous doses of 4.4, 13.3, & 40 mg/kg, decreased pup survival was observed at the high dose. The high dose is comparable to the daily MRHD of 400 mg/day on a BSA basis.

Labor and Delivery: SEE BOXED WARNING REGARDING OBSTETRICAL USE OF 0.75% BUPIVACAINE HYDROCHLORIDE.

Bupivacaine Hydrochloride is contraindicated for obstetrical paracervical block anesthesia.

Local anesthetics rapidly cross the placenta, and when used for epidural, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, fetal, and neonatal toxicity. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.) 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 has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient’s legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously and electronic fetal monitoring is highly advisable.

Epidural, caudal, or pudendal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Epidural anesthesia has been reported to prolong the second stage of labor by removing the parturient’s reflex urge to bear down or by interfering with motor function. The use of obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may be followed by diminished muscle strength and tone for the first day or two of life. This has not been reported with bupivacaine.

It is extremely important to avoid aortocaval compression by the gravid uterus during administration of regional block to parturients. To do this, the patient must be maintained in the left lateral decubitus position or a blanket roll or sandbag may be placed beneath the right hip and gravid uterus displaced to the left.

Nursing Mothers: Bupivacaine has been reported to be excreted in human milk suggesting that the nursing infant could be theoretically exposed to a dose of the drug. Because of the potential for serious adverse reactions in nursing infants from bupivacaine, a decision should be made whether to discontinue nursing or not administer bupivacaine, taking into account the importance of the drug to the mother.

Pediatric Use: Until further experience is gained in pediatric patients younger than 12 years, administration of Bupivacaine Hydrochloride in this age group is not recommended. Continuous infusions of bupivacaine in children have been reported to result in high systemic levels of bupivacaine and seizures; high plasma levels may also be associated with cardiovascular abnormalities. (See WARNINGS, PRECAUTIONS, and OVERDOSAGE.)

Geriatric Use: Patients over 65 years, particularly those with hypertension, may be at increased risk for developing hypotension while undergoing anesthesia with Bupivacaine Hydrochloride. (See ADVERSE REACTIONS.)

Elderly patients may require lower doses of Bupivacaine Hydrochloride. (See PRECAUTIONS, Epidural Anesthesia and DOSAGE AND ADMINISTRATION.)

In clinical studies, differences in various pharmacokinetic parameters have been observed between elderly and younger patients. (See CLINICAL PHARMACOLOGY.)

This product is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See CLINICAL PHARMACOLOGY.)

ADVERSE REACTIONS

Reactions to Bupivacaine Hydrochloride are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, unintentional intravascular injection, or slow metabolic degradation.

The most commonly encountered acute adverse experiences which demand immediate counter-measures are related to the central nervous system and the cardiovascular system. These adverse experiences are generally dose related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance, or from unintentional intravascular injection of the local anesthetic solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection of drug during the intended performance of caudal or lumbar epidural block or nerve blocks
near the vertebral column (especially in the head and neck region) may result in underventilation or
apnea (“Total or High Spinal”). Also, hypotension due to loss of sympathetic tone and respiratory
paralysis or underventilation due to cephalad extension of the motor level of anesthesia may occur. This
may lead to secondary cardiac arrest if untreated. Patients over 65 years, particularly those with
hypertension, may be at increased risk for experiencing the hypotensive effects of Bupivacaine
Hydrochloride. Factors influencing plasma protein binding, such as acidosis, systemic diseases which
alter protein production, or competition of other drugs for protein binding sites, may diminish individual
tolerance.

Central Nervous System Reactions: These are characterized by excitation and/or depression.
Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to
convulsions. However, excitement may be transient or absent, with depression being the first
manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into
unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting,
chills, and constriction of the pupils.

The incidence of convulsions associated with the use of local anesthetics varies with the procedure
used and the total dose administered. In a survey of studies of epidural anesthesia, overt toxicity
progressing to convulsions occurred in approximately 0.1% of local anesthetic administrations.

Cardiovascular System Reactions: High doses or unintentional intravascular injection may lead to high
plasma levels and related depression of the myocardium, decreased cardiac output, heartblock,
hypotension, bradycardia, ventricular arrhythmias, including ventricular tachycardia and ventricular
fibrillation, and cardiac arrest. (See WARNINGS, PRECAUTIONS, and OVERDOSAGE sections.)

Allergic: Allergic-type reactions are rare and may occur as a result of sensitivity to the local anesthetic
or to other formulation ingredients, such as the antimicrobial preservative methylparaben contained in
multiple-dose vials or sulfites in epinephrine-containing solutions. These reactions are characterized
by signs such as urticaria, pruritus, 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 has been reported. The usefulness of
screening for sensitivity has not been definitely established.

Neurologic: The incidences of adverse neurologic reactions associated with the use of local
anesthetics may be related to the total dose of local 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 a contribution from the drug.

In the practice of caudal or lumbar epidural block, occasional unintentional penetration of the
subarachnoid space by the catheter or needle may occur. Subsequent adverse effects may depend
partially on the amount of drug administered intrathecally and the physiological and physical effects of a
dural puncture. A high spinal is characterized by paralysis of the legs, loss of consciousness,
respiratory paralysis, and bradycardia.

Neurologic effects following epidural or caudal anesthesia may include spinal block of varying
magnitude (including high or total spinal block); hypotension secondary to spinal block; urinary
retention; fecal and urinary incontinence; loss of perineal sensation and sexual function; persistent
anesthesia, paresthesia, weakness, paralysis of the lower extremities and loss of sphincter control all of
which may have slow, incomplete, or no recovery; headache; backache; septic meningitis; meningismus;
slowing of labor; increased incidence of forceps delivery; and cranial nerve palsies due to traction on
nerves from loss of cerebrospinal fluid.

Neurologic effects following other procedures or routes of administration may include persistent
anesthesia, paresthesia, weakness, paralysis, all of which may have slow, incomplete, or no recovery.

OVERDOSAGE
Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid injection of local anesthetic solution. (See ADVERSE REACTIONS, WARNINGS, and PRECAUTIONS.)

Management of Local Anesthetic Emergencies: The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient’s state of consciousness after each local anesthetic injection. 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 the convulsions. A 50 mg to 100 mg bolus IV injection of succinylcholine will paralyze the patient without depressing the central nervous or cardiovascular systems and facilitate ventilation. A bolus IV dose of 5 mg to 10 mg of diazepam or 50 mg to 100 mg of thiopental will permit ventilation and counteract central nervous system stimulation, but these drugs also depress central nervous system, respiratory, and cardiac function, add to postictal depression and may result in apnea. Intravenous barbiturates, anticonvulsant 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).

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

Recent clinical data from patients experiencing local anesthetic-induced convulsions demonstrated rapid development of hypoxia, hypercarbia, and acidosis with bupivacaine within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

If not treated immediately, convulsions with simultaneous hypoxia, hypercarbia, and acidosis plus myocardial depression from the direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities, including apnea, may occur. Underventilation or apnea due to unintentional subarachnoid injection of local anesthetic solution may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest should occur, successful outcome may require prolonged resuscitative efforts.

The supine position is dangerous in pregnant women at term because of aortocaval 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 be accomplished.

The mean seizure dosage of bupivacaine in rhesus monkeys was found to be 4.4 mg/kg with mean arterial plasma concentration of 4.5 mcg/mL. The intravenous and subcutaneous LD50 in mice is 6 mg/kg to 8 mg/kg and 38 mg/kg to 54 mg/kg respectively.

**DOSAGE AND ADMINISTRATION**

The dose of any local anesthetic administered varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of
anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual
tolerance, and the physical condition of the patient. The smallest dose and concentration required to
produce the desired result should be administered. Dosages of Bupivacaine Hydrochloride should be
reduced for elderly and/or debilitated patients and patients with cardiac and/or liver disease. The rapid
injection of a large volume of local anesthetic solution should be avoided and fractional (incremental)
doses should be used when feasible.

For specific techniques and procedures, refer to standard textbooks.

There have been adverse event reports of chondrolysis in patients receiving intra-articular infusions of
local anesthetics following arthroscopic and other surgical procedures. Bupivacaine Hydrochloride is
not approved for this use (see WARNINGS and DOSAGE AND ADMINISTRATION).

In recommended doses, Bupivacaine Hydrochloride produces complete sensory block, but the effect on
motor function differs among the three concentrations.

0.25% ─ when used for caudal, epidural, or peripheral nerve block, produces incomplete motor block.
Should be used for operations in which muscle relaxation is not important, or when another means of
providing muscle relaxation is used concurrently. Onset of action may be slower than with the 0.5% or
0.75% solutions.

0.5% ─ provides motor blockade for caudal, epidural, or nerve block, but muscle relaxation may be
inadequate for operations in which complete muscle relaxation is essential.

0.75% ─ produces complete motor block. Most useful for epidural block in abdominal operations
requiring complete muscle relaxation, and for retrobulbar anesthesia. Not for obstetrical anesthesia.

The duration of anesthesia with Bupivacaine Hydrochloride is such that for most indications, a single
dose is sufficient.

Maximum dosage limit must be individualized in each case after evaluating the size and physical status
of the patient, as well as the usual rate of systemic absorption from a particular injection site. Most
experience to date is with single doses of Bupivacaine Hydrochloride up to 225 mg with epinephrine
1:200,000 and 175 mg without epinephrine; more or less drug may be used depending on
individualization of each case.

These doses may be repeated up to once every three hours. In clinical studies to date, total daily doses
have been up to 400 mg. Until further experience is gained, this dose should not be exceeded in 24
hours. The duration of anesthetic effect may be prolonged by the addition of epinephrine.

The dosages in Table 1 have generally proved satisfactory and are recommended as a guide for use in
the average adult. These dosages should be reduced for elderly or debilitated patients. Until further
experience is gained, Bupivacaine Hydrochloride is not recommended for pediatric patients younger
than 12 years. Bupivacaine Hydrochloride is contraindicated for obstetrical paracervical blocks, and is
not recommended for intravenous regional anesthesia (Bier Block).

Use in Epidural Anesthesia: During epidural administration of Bupivacaine Hydrochloride, 0.5% and
0.75% solutions should be administered in incremental doses of 3 mL to 5 mL with sufficient time
between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. In
obstetrics, only the 0.5% and 0.25% concentrations should be used; incremental doses of 3 mL to 5 mL
of the 0.5% solution not exceeding 50 mg to 100 mg at any dosing interval are recommended. Repeat
doses should be preceded by a test dose containing epinephrine if not contraindicated. Use only the
single-dose ampuls and single-dose vials for caudal or epidural anesthesia; the multiple-dose vials
contain a preservative and therefore should not be used for these procedures.

Test Dose for Caudal and Lumbar Epidural Blocks: The Test Dose of Bupivacaine Hydrochloride
(0.5% bupivacaine with 1:200,000 epinephrine in a 3 mL ampul) is recommended for use as a test dose
when clinical conditions permit prior to caudal and lumbar epidural blocks. This may serve as a warning
of unintended intravascular or subarachnoid injection. (See PRECAUTIONS.) The pulse rate and other
signs should be monitored carefully immediately following each test dose administration to detect possible intravascular injection, and adequate time for onset of spinal block should be allotted to detect possible intrathecal injection. An intravascular or subarachnoid injection is still possible even if results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, high spinal or cardiovascular effects from the epinephrine. (See WARNINGS and OVERDOSAGE.)

Unused portions of solution not containing preservatives, i.e., those supplied in single-dose ampuls and single-dose vials, should be discarded following initial use.

This product should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions which are discolored or which contain particulate matter should not be administered.

<table>
<thead>
<tr>
<th>Table 1. Recommended Concentrations and Doses of Bupivacaine Hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Block</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Local infiltration</td>
</tr>
<tr>
<td>Epidural</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Caudal</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Peripheral nerves</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Retrobulbar3</td>
</tr>
<tr>
<td>Sympathetic</td>
</tr>
<tr>
<td>Epidural3</td>
</tr>
</tbody>
</table>

1 With continuous (intermittent) techniques, repeat doses increase the degree of motor block. The first repeat dose of 0.5% may produce complete motor block. Intercostal nerve block with 0.25% may also produce complete motor block for intra-abdominal surgery.
2 For single-dose use, not for intermittent epidural technique. Not for obstetrical anesthesia.
3 See PRECAUTIONS.
4 Solutions with or without epinephrine.
HOW SUPPLIED

These solutions are not for spinal anesthesia.

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

Bupivacaine Hydrochloride — Solutions of Bupivacaine Hydrochloride that do not contain epinephrine may be autoclaved. Autoclave at 15-pound pressure, 121°C (250°F) for 15 minutes. Do not autoclave product packaged in Abboject™ Syringes.

<table>
<thead>
<tr>
<th>NDC No.</th>
<th>Conc.</th>
<th>Size</th>
<th>pH</th>
<th>Package</th>
</tr>
</thead>
<tbody>
<tr>
<td>0409-1158-01</td>
<td>0.25%</td>
<td>30 mL</td>
<td>4.0 to 6.5</td>
<td>Ampul</td>
</tr>
<tr>
<td>0409-1158-02</td>
<td>0.25%</td>
<td>50 mL</td>
<td>4.0 to 6.5</td>
<td>Ampul</td>
</tr>
<tr>
<td>0409-1159-01</td>
<td>0.25% 10 mL</td>
<td>4.0 to 6.5</td>
<td>Teartop Vial</td>
<td></td>
</tr>
<tr>
<td>0409-1159-02</td>
<td>0.25% 30 mL</td>
<td>4.0 to 6.5</td>
<td>Teartop Vial</td>
<td></td>
</tr>
<tr>
<td>0409-1160-01</td>
<td>0.25% 50 mL</td>
<td>4.0 to 6.5</td>
<td>Fliptop Vial (Multiple-dose)</td>
<td></td>
</tr>
<tr>
<td>0409-1161-01</td>
<td>0.5% 30 mL</td>
<td>4.0 to 6.5</td>
<td>Ampul</td>
<td></td>
</tr>
<tr>
<td>0409-1163-01</td>
<td>0.5% 50 mL</td>
<td>4.0 to 6.5</td>
<td>Fliptop Vial (Multiple-dose)</td>
<td></td>
</tr>
<tr>
<td>0409-1162-01</td>
<td>0.5% 10 mL</td>
<td>4.0 to 6.5</td>
<td>Teartop Vial</td>
<td></td>
</tr>
<tr>
<td>0409-1162-02</td>
<td>0.5% 30 mL</td>
<td>4.0 to 6.5</td>
<td>Teartop Vial</td>
<td></td>
</tr>
<tr>
<td>0409-1165-01</td>
<td>0.75% 10 mL</td>
<td>4.0 to 6.5</td>
<td>Teartop Vial</td>
<td></td>
</tr>
<tr>
<td>0409-1165-02</td>
<td>0.75% 30 mL</td>
<td>4.0 to 6.5</td>
<td>Teartop Vial</td>
<td></td>
</tr>
<tr>
<td>0409-5622-01</td>
<td>0.25% 30 mL</td>
<td>4.0 to 6.5</td>
<td>Ampul</td>
<td></td>
</tr>
<tr>
<td>0409-5623-02</td>
<td>0.75% 2 mL</td>
<td>4.0 to 6.5</td>
<td>Ampul</td>
<td></td>
</tr>
<tr>
<td>0409-5757-01</td>
<td>0.5% 20 mL</td>
<td>4.0 to 6.5</td>
<td>Ampul</td>
<td></td>
</tr>
<tr>
<td>0409-5758-01</td>
<td>0.5% 20 mL</td>
<td>4.0 to 6.5</td>
<td>AbbojectTM Syringe</td>
<td></td>
</tr>
</tbody>
</table>

Bupivacaine Hydrochloride with epinephrine 1:200,000 (as bitartrate)—Solutions of Bupivacaine Hydrochloride that contain epinephrine should not be autoclaved and should be protected from light. Do not use the solution if its color is pinkish or darker than slightly yellow or if it contains a precipitate.

<table>
<thead>
<tr>
<th>NDC No.</th>
<th>Concentration Bupivacaine HCl</th>
<th>Size</th>
<th>pH</th>
<th>Package</th>
</tr>
</thead>
<tbody>
<tr>
<td>0409-9042-01</td>
<td>0.25%</td>
<td>10 mL</td>
<td>3.3 to 5.5</td>
<td>Teartop Vial</td>
</tr>
<tr>
<td>0409-9042-02</td>
<td>0.25%</td>
<td>30 mL</td>
<td>3.3 to 5.5</td>
<td>Teartop Vial</td>
</tr>
<tr>
<td>0409-9042-17</td>
<td>0.25%</td>
<td>30 mL</td>
<td>3.3 to 5.5</td>
<td>Teartop Vial</td>
</tr>
<tr>
<td>0409-9043-01</td>
<td>0.25%</td>
<td>50 mL</td>
<td>3.3 to 5.5</td>
<td>Fliptop Vial (Multiple-dose)</td>
</tr>
<tr>
<td>0409-9045-01</td>
<td>0.5%</td>
<td>10 mL</td>
<td>3.3 to 5.5</td>
<td>Teartop Vial</td>
</tr>
<tr>
<td>0409-9045-02</td>
<td>0.5%</td>
<td>30 mL</td>
<td>3.3 to 5.5</td>
<td>Teartop Vial</td>
</tr>
<tr>
<td>0409-9045-17</td>
<td>0.5%</td>
<td>30 mL</td>
<td>3.3 to 5.5</td>
<td>Teartop Vial</td>
</tr>
<tr>
<td>0409-9046-01</td>
<td>0.5%</td>
<td>50 mL</td>
<td>3.3 to 5.5</td>
<td>Fliptop Vial (Multiple-dose)</td>
</tr>
</tbody>
</table>

Revised: 01/2013

Abboject™ is a registered trademark of the Abbott group of companies.

EN-3180
Drug Facts

3M DURAPREP SURGICAL (iodine povacrylex and isopropyl alcohol) solution

[3M Health Care]

Drug Facts

Active ingredients

Iodine povacrylex (0.7% available iodine)
Isopropyl alcohol, 74% w/w

Purpose

Antiseptic

Uses

Patient preoperative skin preparation:

For preparation of the skin prior to surgeryhelps reduce bacteria that potentially can cause skin infection

Warnings

For external use only. Flammable, keep away from fire or flame.

To reduce the risk of fire, PREP CAREFULLY:

Solution contains alcohol and gives off flammable vaporsdo not drape or use ignition source (e.g., cautery, laser) until solution is completely dry (minimum of 3 minutes on hairless skin; up to 1 hour in hair). Avoid getting solution into hairy areas. Wet hair is flammable. Hair may take up to 1 hour to dry. Do not allow solution to poolremove solution-stained material from prep area

Do not use

On patients with known allergies to iodine or any other ingredients in this producton open wounds, on mucous membranes, or as a general skin cleanserin infants less than 2 months old due to the risk of excessive skin irritation and transient hypothyroidism
When using this product keep out of eyes, ears, and mouth. May cause serious injury if permitted to enter and remain. If contact occurs, flush with cold water right away and contact a doctor. To avoid skin injury, care should be taken when removing drapes, tapes, etc…applied over film use with caution in women who are breast-feeding due to the potential for transient hypothyroidism in the nursing newborn.

Stop use and ask a doctor if irritation, sensitization or allergic reaction occurs. These may be signs of a serious condition. On rare occasions, use of this product has been associated with skin blistering.

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions (follow all directions for use)

At the end of the prep, discard any portion of the solution which is not required to cover the prep area. It is not necessary to use the entire amount available.

Getting Patient Ready for Solution:

Use in well-ventilated area do not microwave or heat the solution applicator apply to clean, completely dry, residue-free, intact skin when hair removal is necessary, use a surgical clipper on the morning of the surgery. If a wet shave is used, thoroughly remove all soap residues.

Activating the Applicator:

Grasp product by wrapping hand and fingers around the labeled portion of the applicator. Place thumb on the lever. With sponge face parallel to the floor, snap lever. Allow all fluid to flow into sponge.

When Applying Solution:

Do not scrub. Paint a single, uniform application and do not reprep area. Do not allow solution to pool. Use sponge applicator to absorb excess solution and continue to apply a uniform coating. If solution accidentally gets outside of prep area, remove excess with gauze. Tuck prep towels as needed under both sides of the neck to absorb excess solution. Remove towels before draping. Avoid getting solution into hairy areas. Wet hair is flammable. Hair may take up to 1 hour to dry. When prepping skin folds, toes, or fingers, use a sterile-gloved hand to hold skin apart until completely dry. Otherwise, skin may adhere to itself.

After Applying Solution:

To reduce the risk of fire, wait until solution is completely dry (minimum of 3 minutes on hairless skin; up to 1 hour in hair). Solution will turn from a shiny to a dull appearance on skin alerting the user that the solution is completely dry and no longer flammable.

While Waiting for Solution to Completely Dry:

Do not drape or use ignition source (e.g., cautery, laser) check for pooled solution. Use sterile gauze to soak up pooled solution. Do not blot because it may remove solution from skin. Remove solution-stained materials. Replace if necessary.

After Solution is Completely Dry:

To reduce the risk of fire, begin draping and/or using cautery only after solution is completely dry and all solution-stained materials are removed. If incise drapes are used, apply directly to dry prep. On completion of surgical procedure, removal of incise drape will remove film. Apply dressing following
standard practices

Other information

store between 20-25°C (68-77°F) avoid excessive heat above 40°C (104°F). Solution is not water soluble and may stain. Therefore, avoid contact with reusable items (basins, instruments).

Inactive ingredients

ethyl alcohol, water

Questions?
call 1-800-228-3957 (Monday to Friday 7AM – 6PM CST). www.3M.com.

Package Label Display Panel
## Product Information

**Product Type**: MEDICAL DEVICE  
**Item Code (Source)**: NHRIC:51688-6270

### Packaging

<table>
<thead>
<tr>
<th>#</th>
<th>Item Code</th>
<th>Package Description</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NHRIC:51688-6270-2</td>
<td>10 in 1 CASE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>1 in 1 PACKAGE, COMBINATION</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Quantity of Parts

<table>
<thead>
<tr>
<th>Part #</th>
<th>Package Quantity</th>
<th>Total Product Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1</td>
<td>1 AMPULE</td>
<td>5 mL</td>
</tr>
<tr>
<td>Part 2</td>
<td>1 AMPULE</td>
<td>10 mL</td>
</tr>
<tr>
<td>Part 3</td>
<td>1 AMPULE</td>
<td>5 mL</td>
</tr>
<tr>
<td>Part 4</td>
<td>1 APPLICATOR</td>
<td>6 mL</td>
</tr>
<tr>
<td>Part 5</td>
<td>1 AMPULE</td>
<td>2 mL</td>
</tr>
<tr>
<td>Part 6</td>
<td>1 AMPULE</td>
<td>20 mL</td>
</tr>
</tbody>
</table>
LIDOCAINE HYDROCHLORIDE
lidocaine hydrochloride injection, solution

Product Information
Item Code (Source)  NDC:0409-4713
Route of Administration  INFILTRATION, SUBCUTANEOUS

Active Ingredient/Active Moiety
<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIDOCAINE HYDROCHLORIDE (UNII: V13007Z41A) (LIDOCAINE - UNII9F2Z00987)</td>
<td>LIDOCAINE HYDROCHLORIDE ANHYDROUS</td>
<td>10 mg in 1 mL</td>
</tr>
</tbody>
</table>

Inactive Ingredients
<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Chloride (UNII: 451W47IQ8X)</td>
<td>7 mg in 1 mL</td>
</tr>
<tr>
<td>Water (UNII: 059QF0KO0R)</td>
<td></td>
</tr>
<tr>
<td>Sodium Hydroxide (UNII: 55X04QC32I)</td>
<td></td>
</tr>
<tr>
<td>Hydrochloric Acid (UNII: QTT17582CB)</td>
<td></td>
</tr>
</tbody>
</table>

Packaging
<table>
<thead>
<tr>
<th>#</th>
<th>Item Code</th>
<th>Package Description</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NDC:0409-4713-65</td>
<td>5 mL in 1 AMPULE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Marketing Information
<table>
<thead>
<tr>
<th>Marketing Category</th>
<th>Application Number or Monograph Citation</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANDA</td>
<td>ANDA080408</td>
<td>03/30/2010</td>
<td></td>
</tr>
</tbody>
</table>

SODIUM CHLORIDE
sodium chloride solution

Product Information
Item Code (Source)  NDC:65282-1510
Route of Administration  EPIDURAL
### Active Ingredient/Active Moiety

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>SODIUM CHLORIDE (UNII: 451W47Q8X) (SODIUM CATION - UNII:LYR4M0NH37, CHLORIDE ION - UNII:Q32ZN48698)</td>
<td>SODIUM CHLORIDE</td>
<td>9 mg in 1 mL</td>
</tr>
</tbody>
</table>

### Inactive Ingredients

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>WATER (UNII: 059QF0KO0R)</td>
<td></td>
</tr>
</tbody>
</table>

### Packaging

<table>
<thead>
<tr>
<th>#</th>
<th>Item Code</th>
<th>Package Description</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NDC:65282-1510-1</td>
<td>10 mL in 1 AMPULE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Marketing Information

<table>
<thead>
<tr>
<th>Marketing Category</th>
<th>Application Number or Monograph Citation</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>unapproved drug other</td>
<td></td>
<td>12/01/2000</td>
<td></td>
</tr>
</tbody>
</table>

### Part 3 of 6

**LIDOCAINE HYDROCHLORIDE AND EPINEPHRINE**

Lidocaine hydrochloride anhydrous and epinephrine injection, solution

### Product Information

<table>
<thead>
<tr>
<th>Item Code (Source)</th>
<th>NDC:0409-1209</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of Administration</td>
<td>EPIDURAL, INFILTRATION</td>
</tr>
</tbody>
</table>

### Active Ingredient/Active Moiety

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIDOCAINE HYDROCHLORIDE (UNII: V13007Z41A) (LIDOCAINE - UNII:98PI200987)</td>
<td>LIDOCAINE HYDROCHLORIDE ANHYDROUS</td>
<td>15 mg in 1 mL</td>
</tr>
<tr>
<td>EPINEPHRINE (UNII: YKH834O4BH) (EPINEPHRINE - UNII:YKH834O4BH)</td>
<td>EPINEPHRINE</td>
<td>5 ug in 1 mL</td>
</tr>
</tbody>
</table>

### Inactive Ingredients

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>SODIUM METABISULFITE (UNII: 4V0NS5FNS3C)</td>
<td>0.5 mg in 1 mL</td>
</tr>
<tr>
<td>ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)</td>
<td>0.2 mg in 1 mL</td>
</tr>
<tr>
<td>SODIUM HYDROXIDE (UNII: 55X04QC32I)</td>
<td></td>
</tr>
<tr>
<td>HYDROCHLORIC ACID (UNII: QTT17582CB)</td>
<td></td>
</tr>
<tr>
<td>WATER (UNII: 059QF0KO0R)</td>
<td></td>
</tr>
</tbody>
</table>
### Packaging

<table>
<thead>
<tr>
<th>#</th>
<th>Item Code</th>
<th>Package Description</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NDC:0409-1209-65</td>
<td>5 mL in 1 AMPULE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Marketing Information

<table>
<thead>
<tr>
<th>Marketing Category</th>
<th>Application Number or Monograph Citation</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANDA</td>
<td>ANDA088571</td>
<td>04/05/2010</td>
<td></td>
</tr>
</tbody>
</table>

### Part 4 of 6

**3M DURAPREP SURGICAL**

iodine povacrylex and isopropyl alcohol solution

### Product Information

<table>
<thead>
<tr>
<th>Item Code (Source)</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDC:17518-011</td>
<td>TOPICAL</td>
</tr>
</tbody>
</table>

### Active Ingredient/Active Moiety

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodine povacrylex (UNII: 6E43AWY083) (Iodine - UNII:9679TC07X4)</td>
<td>Iodine</td>
<td>7 mg in 1 mL</td>
</tr>
<tr>
<td>Isopropyl alcohol (UNII: ND2M416302) (Isopropyl alcohol - UNII:ND2M416302)</td>
<td>Isopropyl alcohol</td>
<td>636.4 mg in 1 mL</td>
</tr>
</tbody>
</table>

### Inactive Ingredients

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>water (UNII: 059QF0KO0R)</td>
<td></td>
</tr>
</tbody>
</table>

### Packaging

<table>
<thead>
<tr>
<th>#</th>
<th>Item Code</th>
<th>Package Description</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NDC:17518-011-09</td>
<td>6 mL in 1 APPLICATOR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Marketing Information

<table>
<thead>
<tr>
<th>Marketing Category</th>
<th>Application Number or Monograph Citation</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA</td>
<td>NDA021586</td>
<td>09/29/2006</td>
<td></td>
</tr>
</tbody>
</table>

### Part 5 of 6
## Product Information

<table>
<thead>
<tr>
<th>Item Code (Source)</th>
<th>NDC: 0409-3613</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of Administration</td>
<td>EPIDURAL, INFILTRATION</td>
</tr>
</tbody>
</table>

## Active Ingredient/Active Moiety

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUPIVACAINE HYDROCHLORIDE (UNII: 7TQO7W3VT8) (BUPIVACAINE - UNII: Y8335394RO)</td>
<td>BUPIVACAINE HYDROCHLORIDE ANHYDROUS</td>
<td>7.5 mg in 1 mL</td>
</tr>
</tbody>
</table>

## Inactive Ingredients

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>SODIUM HYDROXIDE (UNII: 55X04QC32I)</td>
<td></td>
</tr>
<tr>
<td>HYDROCHLORIC ACID (UNII: QTT17582CB)</td>
<td></td>
</tr>
<tr>
<td>ANHYDROUS DEXTROSE (UNII: 5SL0G7R0OK)</td>
<td>82.5 mg in 1 mL</td>
</tr>
</tbody>
</table>

## Packaging

<table>
<thead>
<tr>
<th>#</th>
<th>Item Code</th>
<th>Package Description</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NDC: 0409-3613-01</td>
<td>2 mL in 1 AMPULE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Marketing Information

<table>
<thead>
<tr>
<th>Marketing Category</th>
<th>Application Number or Monograph Citation</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANDA</td>
<td>ANDA071810</td>
<td>03/23/2010</td>
<td></td>
</tr>
</tbody>
</table>

## Part 6 of 6

**BUPIVACAINE HYDROCHLORIDE**

bupivacaine hydrochloride injection, solution

---

**Product Information**

<table>
<thead>
<tr>
<th>Item Code (Source)</th>
<th>NDC: 0409-5757</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of Administration</td>
<td>EPIDURAL</td>
</tr>
</tbody>
</table>

## Active Ingredient/Active Moiety

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Inactive Ingredients**

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>WATER (UNII: 059QF0KO0R)</td>
<td></td>
</tr>
<tr>
<td>SODIUM HYDROXIDE (UNII: 55X04QC32I)</td>
<td></td>
</tr>
<tr>
<td>HYDROCHLORIC ACID (UNII: QTT17582CB)</td>
<td></td>
</tr>
<tr>
<td>SODIUM CHLORIDE (UNII: 451W47IQ8X)</td>
<td>8.1 mg in 1 mL</td>
</tr>
</tbody>
</table>

**Packaging**

<table>
<thead>
<tr>
<th>#</th>
<th>Item Code</th>
<th>Package Description</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NDC:0409-5757-01</td>
<td>20 mL in 1 AMPULE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Marketing Information**

<table>
<thead>
<tr>
<th>Marketing Category</th>
<th>Application Number or Monograph Citation</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA</td>
<td>NDA018053</td>
<td>05/19/2010</td>
<td></td>
</tr>
<tr>
<td>premarket notification</td>
<td>K965017</td>
<td>02/08/2012</td>
<td></td>
</tr>
</tbody>
</table>

**Labeler** - Smiths Medical ASD, Inc. (137835299)

**Establishment**

<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
<th>ID/FEI</th>
<th>Business Operations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smiths Medical ASD, Inc.</td>
<td></td>
<td>137835299</td>
<td>manufacture</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
<th>ID/FEI</th>
<th>Business Operations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospira, Inc.</td>
<td>030606222</td>
<td></td>
<td>manufacture</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
<th>ID/FEI</th>
<th>Business Operations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospira, Inc.</td>
<td>093132819</td>
<td></td>
<td>manufacture</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
<th>ID/FEI</th>
<th>Business Operations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwang Myung Pharm. Co., Ltd.</td>
<td></td>
<td>631099384</td>
<td>manufacture</td>
</tr>
<tr>
<td>Name</td>
<td>Address</td>
<td>ID/FEI</td>
<td>Business Operations</td>
</tr>
<tr>
<td>------------</td>
<td>---------</td>
<td>---------</td>
<td>---------------------</td>
</tr>
<tr>
<td>3M Company</td>
<td></td>
<td>078671244</td>
<td>manufacture</td>
</tr>
</tbody>
</table>

Revised: 8/2014

Smiths Medical ASD, Inc.