

**H-PAXIN- lidocaine hydrochloride, bupivacaine hydrochloride, betamethasone sodium phosphate and betamethasone acetate**  
**IT3 Medical LLC**

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**H-Paxin Injection System**

**Lidocaine Hydrochloride Injection, USP**

**AQUEOUS SOLUTIONS FOR  
INFILTRATION AND NERVE BLOCK**

**Ampul**

**Plastic Multiple-dose Fliptop Vial**

**Glass Teartop Vial**

**Rx only**

**DESCRIPTION**

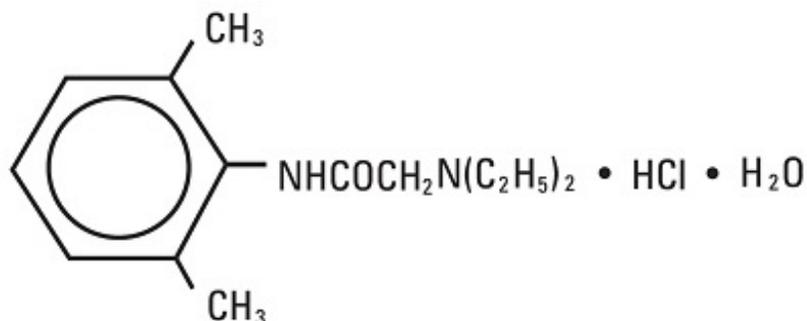
Lidocaine Hydrochloride Injection, USP is a sterile, nonpyrogenic solution of lidocaine hydrochloride in water for injection for parenteral administration in various concentrations with characteristics as follows:

<b>Concentration</b>	<b>0.5%</b>	<b>1%</b>	<b>1.5%</b>	<b>2%</b>
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:



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 HCl 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 HCl 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 HCl 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 HCl is protein bound. Binding is also dependent on the plasma concentration of the alpha-1-acid glycoprotein.

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

Lidocaine HCl 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 HCl. Approximately 90% of lidocaine HCl 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 HCl following an intravenous bolus injection is typically 1.5 to 2 hours. Because of the rapid rate at which lidocaine HCl is metabolized, any condition that affects liver function may alter lidocaine HCl kinetics. The half-life may be prolonged two-fold or more in patients with liver dysfunction. Renal dysfunction does

not affect lidocaine HCl 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 HCl required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6 mcg free base per mL. In the rhesus monkey arterial blood levels of 18 to 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 HCl 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.

Anaphylactic reactions may occur following administration of lidocaine hydrochloride (see **ADVERSE REACTIONS**).

In the case of severe reaction, discontinue the use of the drug.

## **PRECAUTIONS**

### **General**

The safety and effectiveness of lidocaine HCl 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 HCl 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 HCl 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 HCl 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 HCl.

### **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 anti-depressants 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 HCl 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 HCl.

## **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

## **Pregnancy**

### **Teratogenic Effects**

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 HCl. 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 HCl 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 and Metabolism**). 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 a 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 HCl is administered to a nursing woman.

## **Pediatric Use**

Dosages in children 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 HCl 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 HCl 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 the multiple dose vials. Allergic reactions, including anaphylactic reactions, may occur as a result of sensitivity to lidocaine, but are infrequent. If allergic reactions do occur, they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

There have been no reports of cross sensitivity between lidocaine hydrochloride and procainamide or between lidocaine hydrochloride and quinidine.

### 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 HCl 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.

Hematologic

Methemoglobinemia.

## **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 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 the 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 HCl.

The oral LD<sub>50</sub> of lidocaine HCl in non-fasted female rats is 459 (346 to 773) mg/kg (as the salt) and 214 (159 to 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 the 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 HCl 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:

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1%                    30 mL single-dose teartop vials

1.5%	20 mL single-dose ampuls
2%	10 mL single-dose ampuls

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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 to 3 mL of the indicated concentration per dermatome).

### Caudal and Lumbar Epidural Block

As a precaution against the adverse experience sometimes observed following unintentional penetration of the subarachnoid space, a test dose such as 2 to 3 mL of 1.5% lidocaine HCl 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 to 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 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

**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 to 100 mg (1.5 to 2 mg/lb). The use of even more dilute solutions (i.e., 0.25 to 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.

**NOTE:** 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 1 Recommended Dosages**

Procedure	Lidocaine Hydrochloride Injection, USP (without Epinephrine)		
	Conc. (%)	Vol. (mL)	Total Dose (mg)
<b><i>Infiltration</i></b>			
Percutaneous	0.5 or 1	1 to 60	5 to 300
Intravenous regional	0.5	10 to 60	50 to 300
<b><i>Peripheral Nerve Blocks, e.g.</i></b>			
Brachial	1.5	15 to 20	225 to 300
Dental	2	1 to 5	20 to 100
Intercostal	1	3	30
Paravertebral	1	3 to 5	30 to 50
Pudendal (each side)	1	10	100
Paracervical			
Obstetrical analgesia (each side)	1	10	100
<b><i>Sympathetic Nerve Blocks, e.g.</i></b>			
Cervical (stellate ganglion)	1	5	50
Lumbar	1	5 to 10	50 to 100
<b><i>Central Neural Blocks</i></b>			
Epidural*			
Thoracic	1	20 to 30	200 to 300

Lumbar			
Analgesia	1	25 to 30	250 to 300
Anesthesia	1.5	15 to 20	225 to 300
	2	10 to 15	200 to 300
Caudal			
Obstetrical analgesia	1	20 to 30	200 to 300
Surgical anesthesia	1.5	15 to 20	225 to 300

\* 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 incidents of swelling and edema. When chemical disinfection of multi-dose vials is desired, either isopropyl alcohol (91%) or ethyl alcohol (70%) 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:

Unit of Sale	Concentration	Each
<b>Multiple-dose:</b>		
<b>NDC 0409-4277-02</b> Tray of 25	2% <b>1000 mg/50 mL</b> (20 mg/mL)	NDC 0409-4277-17 Plastic Flip-top Vial

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.**

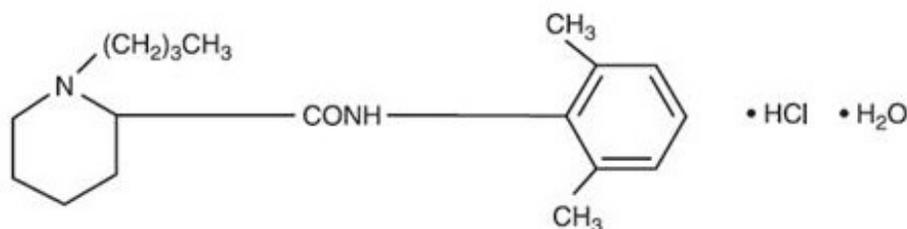
LAB-1118-3.0  
05/2018

### Bupivacaine Hydrochloride Injection, USP

**Rx only**

## 1.1 DESCRIPTION

Bupivacaine hydrochloride USP is 2-Piperidinecarboxamide, 1-butyl-*N*-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate, a white, odorless, 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:



Bupivacaine hydrochloride injection USP is available in sterile isotonic solution for injection via local infiltration, peripheral nerve block, and caudal and lumbar epidural blocks. Solution of bupivacaine hydrochloride injection USP may be autoclaved. Solution is 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 — Sterile isotonic solution containing sodium chloride. In multiple-dose vials, each mL also contains 1 mg methylparaben as antiseptic preservative. The pH of the solution is adjusted to between 4 and 6.5 with sodium hydroxide or hydrochloric acid.

## 1.2 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.

### **1.2.1 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, 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.

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 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 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 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 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 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.

### 1.3 INDICATIONS AND USAGE

Bupivacaine hydrochloride injection USP is indicated for the production of local or regional anesthesia or analgesia for surgery, 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 injection USP in these patients.

Bupivacaine hydrochloride injection USP is not recommended for intravenous regional anesthesia (Bier Block). See **WARNINGS**.

The routes of administration and indicated bupivacaine hydrochloride injection USP 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 (see **PRECAUTIONS**)

(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 injection USP.

## 1.4 CONTRAINDICATIONS

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

Bupivacaine hydrochloride injection 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 injection solutions.

## 1.5 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.

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.

## **1.6 PRECAUTIONS**

### **1.6.1 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.

### **1.6.2 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 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.

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.)

### **1.6.3 Use in Head and Neck Area**

Small doses of local anesthetics injected into the head and neck area, including retrobulbar, 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.**)

### **1.6.4 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.

### **1.6.5 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.

### **1.6.6 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.

### **1.6.7 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.

### **1.6.8 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 hydrochloride 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/m<sup>2</sup> 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 mg/kg/day, 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.

### 1.6.9 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.

### 1.6.10 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.

### 1.6.11 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**.)

### 1.6.12 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**.)

## **1.7 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.

### **1.7.1 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.

### **1.7.2 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.**)

### **1.7.3 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. 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.

### **1.7.4 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.

## **1.8 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.**)

### **1.8.1 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 LD<sub>50</sub> in mice is 6 mg/kg to 8 mg/kg and 38 mg/kg to 54 mg/kg respectively.

## 1.9 DOSAGE AND ADMINISTRATION

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

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 injection 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 injection 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 injection 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 injection 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 injection is not recommended for pediatric patients younger than 12 years. Bupivacaine hydrochloride injection is contraindicated for obstetrical paracervical blocks, and is not recommended for intravenous regional anesthesia (Bier Block).

### 1.9.1 Use in Epidural Anesthesia

During epidural administration of bupivacaine hydrochloride injection, 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

See **PRECAUTIONS**

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 1. Recommended Concentrations and Doses of Bupivacaine Hydrochloride Injection**

Type of Block	Conc.	Each Dose		Motor Block <sup>1</sup>
		(mL)	(mg)	
Local infiltration	0.25% <sup>4</sup>	up to max.	up to max.	--
Epidural	0.75% <sup>2,4</sup>	10 to 20	75 to 150	complete
	0.5% <sup>4</sup>	10 to 20	50 to 100	moderate to complete
	0.25% <sup>4</sup>	10 to 20	25 to 50	partial to moderate
Caudal	0.5% <sup>4</sup>	15 to 30	75 to 150	moderate to complete
	0.25% <sup>4</sup>	15 to 30	37.5 to 75	moderate
Peripheral	0.5% <sup>4</sup>	5 to	25 to max	moderate to

nerves	0.5% <sup>4</sup>	max.	25 to max.	complete
	0.25% <sup>4</sup>	5 to max.	12.5 to max.	moderate to complete
Retrobulbar <sup>3</sup>	0.75% <sup>4</sup>	2 to 4	15 to 30	complete
Sympathetic	0.25%	20 to 50	50 to 125	--
Epidural <sup>3</sup> Test Dose	0.5% w/epi	2 to 3	10 to 15 (10 to 15 micrograms epinephrine)	--

<sup>1</sup>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.

<sup>2</sup> For single-dose use, not for intermittent epidural technique. Not for obstetrical anesthesia.

<sup>3</sup> See **PRECAUTIONS**.

<sup>4</sup> Solutions with or without epinephrine.

## 1.10 HOW SUPPLIED

**These solutions are not for spinal anesthesia.**

Bupivacaine Hydrochloride Injection USP — Solution of Bupivacaine hydrochloride injection USP may be autoclaved. Autoclave at 15-pound pressure, 121°C (250°F) for 15 minutes.

Bupivacaine Hydrochloride Injection USP is a clear, colorless, sterile isotonic solution and is available as follows:

Bupivacaine Hydrochloride Injection USP 0.25% (2.5 mg/mL)

50 mL Multiple Dose Vials in a Carton of 25

NDC 55150-249-50

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

The vial stoppers are not made with natural rubber latex.

**Sterile, Nonpyrogenic**

Revised: June 2017

**Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension, USP, 6 mg/mL**

**30 mg/5 mL (6 mg/mL)**

## 2.1 DESCRIPTION

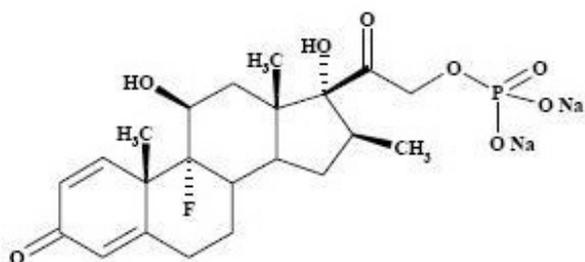
Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension is

a sterile aqueous suspension containing 3 mg per milliliter betamethasone, as betamethasone sodium phosphate, and 3 mg per milliliter betamethasone acetate. Inactive ingredients per mL: 7.1 mg dibasic sodium phosphate anhydrous; 3.4 mg monobasic sodium phosphate monohydrate; 0.1 mg edetate disodium; and 0.2 mg benzalkonium chloride as a preservative. The pH is adjusted to between 6.8 and 7.2.

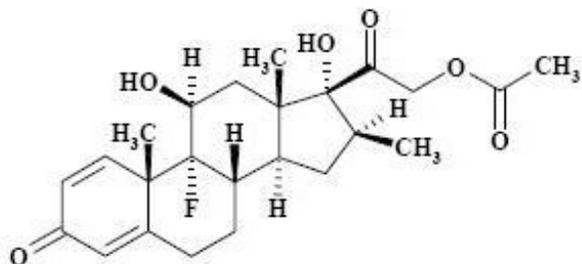
The formula for betamethasone sodium phosphate is  $C_{22}H_{28}FNa_2O_8P$  and it has a molecular weight of 516.40. Chemically, it is 9-Fluoro-11 $\beta$ ,17,21-trihydroxy-16 $\beta$ -methylpregna-1,4-diene-3,20-dione 21-(disodium phosphate).

The formula for betamethasone acetate is  $C_{24}H_{31}FO_6$  and it has a molecular weight of 434.50. Chemically, it is 9-Fluoro-11 $\beta$ ,17,21-trihydroxy-16 $\beta$ -methylpregna-1,4-diene-3,20-dione 21-acetate.

The chemical structures for betamethasone sodium phosphate and betamethasone acetate are as follows:



Structural Formula



Structural Formula

Betamethasone sodium phosphate is a white to practically white, odorless powder, and is hygroscopic. It is freely soluble in water and in methanol, but is practically insoluble in acetone and in chloroform.

Betamethasone acetate is a white to creamy white, odorless powder that sinters and resolidifies at about 165°C, and remelts at about 200°C to 220°C with decomposition. It is practically insoluble in water, but freely soluble in acetone, and is soluble in alcohol and in chloroform.

## 2.2 CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their anti-inflammatory effects in disorders of many organ systems. A derivative of prednisolone, betamethasone has a 16 $\beta$ -methyl group that enhances the anti-inflammatory action of the molecule and reduces the sodium- and water-retaining properties of the fluorine atom bound at carbon 9.

Betamethasone sodium phosphate, a soluble ester, provides prompt activity, while betamethasone acetate is only slightly soluble and affords sustained activity.

## 2.3 INDICATIONS AND USAGE

When oral therapy is not feasible, the **intramuscular use** of Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension is indicated as follows:

**Allergic States** Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, perennial or seasonal allergic rhinitis, serum sickness, transfusion reactions.

**Dermatologic Diseases** Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome).

**Endocrine Disorders** Congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsuppurative thyroiditis.

Hydrocortisone or cortisone is the drug of choice in primary or secondary adrenocortical insufficiency. Synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance.

**Gastrointestinal Diseases** To tide the patient over a critical period of the disease in regional enteritis and ulcerative colitis.

**Hematologic Disorders** Acquired (autoimmune) hemolytic anemia, Diamond-Blackfan anemia, pure red cell aplasia, selected cases of secondary thrombocytopenia.

**Miscellaneous** Trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used with appropriate antituberculous chemotherapy.

**Neoplastic Diseases** For palliative management of leukemias and lymphomas.

**Nervous System** Acute exacerbations of multiple sclerosis; cerebral edema associated with primary or metastatic brain tumor or craniotomy.

**Ophthalmic Diseases** Sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory conditions unresponsive to topical corticosteroids.

**Renal Diseases** To induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome or that due to lupus erythematosus.

**Respiratory Diseases** Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic

eosinophilic pneumonias, symptomatic sarcoidosis.

**Rheumatic Disorders** As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis; acute rheumatic carditis; ankylosing spondylitis; psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). For the treatment of dermatomyositis, polymyositis, and systemic lupus erythematosus.

The **intra-articular or soft tissue administration** of Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute and subacute bursitis, acute nonspecific tenosynovitis, epicondylitis, rheumatoid arthritis, synovitis of osteoarthritis.

The **intralesional administration** of Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension is indicated for alopecia areata; discoid lupus erythematosus; keloids; localized hypertrophic, infiltrated, inflammatory lesions of granuloma annulare, lichen planus, lichen simplex chronicus (neurodermatitis), and psoriatic plaques; necrobiosis lipoidica diabetorum.

Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension may also be useful in cystic tumors of an aponeurosis or tendon (ganglia).

## 2.4 CONTRAINDICATIONS

Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension is contraindicated in patients who are hypersensitive to any components of this product (see **DESCRIPTION**).

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

## 2.5 WARNINGS

Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension should not be administered intravenously.

### 2.5.1 Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

### 2.5.2 General

Rare instances of anaphylactoid/anaphylactic reactions with a possibility of shock have occurred in patients receiving parenteral corticosteroid therapy (see **ADVERSE REACTIONS**). Use caution in patients who have a history of allergic reaction to corticosteroids.

In patients on corticosteroid therapy subjected to any unusual stress, hydrocortisone or cortisone is the drug of choice as a supplement during and after the event.

### 2.5.3 Cardio-Renal

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

### 2.5.4 Endocrine

Corticosteroids can produce reversible hypothalamic pituitary adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

### 2.5.5 Infections

#### 2.5.5.1 General

Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan, or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents. These infections may be mild to severe. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection.

#### 2.5.5.2 Fungal Infections

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see **PRECAUTIONS, Drug Interactions, Amphotericin B Injection and Potassium-Depleting Agents** section).

#### 2.5.5.3 Special Pathogens

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Nocardia*, *Pneumocystis*, and *Toxoplasma*.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating

corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria.

#### *2.5.5.4 Tuberculosis*

The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

#### *2.5.5.5 Vaccination*

**Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted.** Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

#### *2.5.5.6 Viral Infections*

Chickenpox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents should be considered.

### **2.5.6 Neurologic**

Reports of severe medical events have been associated with the intrathecal route of administration (see **ADVERSE REACTIONS, Gastrointestinal and Neurologic/Psychiatric** sections).

Results from one multicenter, randomized, placebo-controlled study with methylprednisolone hemisuccinate, an intravenous corticosteroid, showed an increase in early mortality (at 2 weeks) and late mortality (at 6 months) in patients with cranial trauma who were determined not to have other clear indications for corticosteroid treatment. High doses of corticosteroids, including Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension, should not be used for the treatment of traumatic brain injury.

### **2.5.7 Ophthalmic**

Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Consider referral to an ophthalmologist for patients who develop ocular symptoms or use corticosteroid-containing products for more than 6 weeks. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should not be used in active ocular herpes simplex.

## **2.6 PRECAUTIONS**

### **2.6.1 General**

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

The lowest possible dose of corticosteroid should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

### **2.6.2 Cardio-Renal**

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

### **2.6.3 Endocrine**

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy. Therefore, in any situation of stress occurring during that period, naturally occurring glucocorticoids (hydrocortisone cortisone), which also have salt-retaining properties, rather than betamethasone, are the appropriate choices as replacement therapy in adrenocortical deficiency states.

### **2.6.4 Gastrointestinal**

Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation.

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect of corticosteroids in patients with cirrhosis.

### **2.6.5 Intra-Articular and Soft Tissue Administration**

Intra-articular injected corticosteroids may be systemically absorbed.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Injection of a steroid into an infected site is to be avoided. Local injection of a steroid into a previously injected joint is not usually recommended.

Corticosteroid injection into unstable joints is generally not recommended.

Intra-articular injection may result in damage to joint tissues (see **ADVERSE REACTIONS, Musculoskeletal** section ).

### **2.6.6 Musculoskeletal**

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (i.e., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating corticosteroid therapy.

### **2.6.7 Neuro-Psychiatric**

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect (see **DOSAGE AND ADMINISTRATION**).

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders with neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy of neuromuscular blocking drugs (e.g. pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriplegia. Elevation of creatinine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

## **2.6.8 Information for Patients**

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical attendants that they are taking corticosteroids and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

## **2.6.9 Drug Interactions**

### *Aminoglutethimide*

Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

### *Amphotericin B Injection and Potassium-Depleting Agents*

When corticosteroids are administered concomitantly with potassium-depleting agents (i.e. amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

### *Antibiotics*

Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance.

### *Anticholinesterases*

Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

### *Anticoagulants, Oral*

Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

### *Antidiabetics*

Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

### *Antitubercular Drugs*

Serum concentrations of isoniazid may be decreased.

### *Cholestyramine*

Cholestyramine may increase the clearance of corticosteroids.

### *Cyclosporine*

Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

### *Digitalis Glycosides*

Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

### *Estrogens, Including Oral Contraceptives*

Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

### *Hepatic Enzyme Inducers (e.g., barbiturates, phenytoin, carbamazepine, rifampin)*

Drugs which induce hepatic microsomal drug-metabolizing enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

### *Interactions with Strong CYP3A4 Inhibitors*

Corticosteroids (including betamethasone) are metabolized by CYP3A4.

Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.

Coadministration with other strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin, ritonavir, cobicistat-containing products) may lead to increased exposures of corticosteroids and therefore the potential for increased risk of systemic corticosteroid side effects.

Consider the benefit of coadministration versus the potential risk of systemic corticosteroid effects, in which case patients should be monitored for systemic corticosteroid side effects.

### *Nonsteroidal Anti-inflammatory Agents (NSAIDs)*

Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

### *Skin Tests*

Corticosteroids may suppress reactions to skin tests.

### *Vaccines*

Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Route administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see **WARNINGS, Infections, Vaccination** section).

### **2.6.10 Carcinogenesis, Mutagenesis, Impairment of Fertility**

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

### **2.6.11 Pregnancy**

#### *Teratogenic Effects*

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

### **2.6.12 Nursing Mothers**

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when corticosteroids are administered to a nursing woman.

### **2.6.13 Pediatric Use**

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids, which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (> 2 years of age), and aggressive lymphomas and leukemias (> 1 month of age). Other indications for pediatric use of corticosteroids, e.g., severe asthma and wheezing, are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see **ADVERSE REACTIONS**). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (i.e., cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of

corticosteroids, pediatric patients should be titrated to the lowest effective dose.

### **2.6.14 Geriatric Use**

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and young patients, but greater sensitivity of some older individuals cannot be ruled out.

## **2.7 ADVERSE REACTIONS**

**(listed alphabetically, under each subsection)**

### **Allergic Reactions**

Anaphylactoid reaction, anaphylaxis, angioedema.

### **Cardiovascular**

Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see **WARNINGS**), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

### **Dermatologic**

Acne, allergic dermatitis, cutaneous and subcutaneous atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increased sweating, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

### **Endocrine**

Decreased carbohydrate and glucose tolerance, development of cushingoid state, glucosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

### **Fluid and Electrolyte Disturbances**

Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

### **Gastrointestinal**

Abdominal distention, bowel/bladder dysfunction (after intrathecal administration), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

### **Metabolic**

Negative nitrogen balance due to protein catabolism.

### **Musculoskeletal**

Aseptic necrosis of femoral and humeral heads, calcinosis (following intra-articular or intralesional use), Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, postinjection flare (following intra-articular use), steroid myopathy, tendon rupture, vertebral compression fractures.

### **Neurologic/Psychiatric**

Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration (see **WARNINGS, Neurologic** section).

### **Ophthalmic**

Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, rare instances of blindness associated with periocular injections, vision blurred.

### **Other**

Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, malaise, moon face, weight gain.

## **2.8 OVERDOSAGE**

Treatment of acute overdose is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

## **2.9 DOSAGE AND ADMINISTRATION**

Benzyl alcohol as a preservative has been associated with a fatal Gaspings Syndrome in premature infants and infants of low birth weight. Solutions used for further dilution of this product should be preservative-free when used in the neonate, especially the premature infant. The initial dosage of parenterally administered Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension may vary from 0.25 to 9 mg per day depending on the specific disease entity being treated. However, in certain overwhelming, acute, life-threatening situations, administrations in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

*It Should Be Emphasized That Dosage Requirements Are Variable and Must Be Individualized on the Basis of the Disease Under Treatment and the Response of the Patient.* After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patients individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of the corticosteroid for a period of

time consistent with the patients condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

In the treatment of acute exacerbations of multiple sclerosis, daily doses of 30 mg of betamethasone for a week followed by 12 mg every other day for 1 month are recommended (see **PRECAUTIONS, Neuro-psychiatric** section).

In pediatric patients, the initial dose of betamethasone may vary depending on the specific disease entity being treated. The range of initial doses is 0.02 to 0.3 mg/kg/day in three or four divided doses (0.6 to 9 mg/m<sup>2</sup>bsa/day).

**For the purpose of comparison, the following is the equivalent milligram dosage of the various glucocorticoids:**

Cortisone, 25	Triamcinolone, 4
Hydrocortisone, 20	Paramethasone, 2
Prednisolone, 5	Betamethasone, 0.75
Prednisone, 5	Dexamethasone, 0.75
Methylprednisolone, 4	

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

If coadministration of a local anesthetic is desired, Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension may be mixed with 1% or 2% lidocaine hydrochloride, using the formulations which do not contain parabens. Similar local anesthetics may also be used. Diluents containing methylparaben, propylparaben, phenol, etc., should be avoided, since these compounds may cause flocculation of the steroid. The required dose of Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension is first withdrawn from the vial into the syringe. The local anesthetic is then drawn in, and the syringe shaken briefly. **Do not inject local anesthetics into the vial of Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension.**

### **2.9.1 Bursitis, Tenosynovitis, Peritendinitis**

In acute subdeltoid, subacromial, olecranon, and prepatellar bursitis, one intrabursal injection of 1 mL Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension can relieve pain and restore full range of movement. Several intrabursal injections of corticosteroids are usually required in recurrent acute bursitis and in acute exacerbations of chronic bursitis. Partial relief of pain and some increase in mobility can be expected in both conditions after one or two injections. Chronic bursitis may be treated with reduced dosage once the acute condition is controlled. In tenosynovitis and tendinitis, three or four local injections at intervals of 1 to 2 weeks between injections are given in most cases. Injections should be made into the affected tendon sheaths rather than into the tendons themselves. In ganglions of joint capsules and tendon sheaths, injection of 0.5 mL directly into the ganglion cysts has produced

marked reduction in the size of the lesions.

### 2.9.2 Rheumatoid Arthritis and Osteoarthritis

Following intra-articular administration of 0.5 to 2 mL of Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension, relief of pain, soreness, and stiffness may be experienced. Duration of relief varies widely in both diseases. Intra-articular Injection of Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension is well tolerated in joints and periarticular tissues. There is virtually no pain on injection, and the secondary flare that sometimes occurs a few hours after intra-articular injection of corticosteroids has not been reported with Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension. Using sterile technique, a 20- to 24-gauge needle on an empty syringe is inserted into the synovial cavity and a few drops of synovial fluid are withdrawn to confirm that the needle is in the joint. The aspirating syringe is replaced by a syringe containing Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension and injection is then made into the joint.

#### Recommended Doses for Intra-articular Injection

Size of Joint	Location	Dose (mL)
Very Large	Hip	1-2
Large	Knee, ankle, shoulder	1
Medium	Elbow, wrist	0.5-1
Small (metacarpophalangeal, interphalangeal) (sternoclavicular)	Hand, chest	0.25 to 0.5

A portion of the administered dose of Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension is absorbed systemically following intra-articular injection. In patients being treated concomitantly with oral or parenteral corticosteroids, especially those receiving large doses, the systemic absorption of the drug should be considered in determining intra-articular dosage.

### 2.9.3 Dermatologic Conditions

In intralesional treatment, 0.2 mL/cm<sup>2</sup> of Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension is injected intradermally (not subcutaneously) using a tuberculin syringe with a 25-gauge, 1/2-inch needle. Care should be taken to deposit a uniform depot of medication intradermally. A total of no more than 1 mL at weekly intervals is recommended.

### 2.9.4 Disorders of the Foot

A tuberculin syringe with a 25-gauge, 3/4-inch needle is suitable for most injections into

the foot. The following doses are recommended at intervals of 3 days to a week.

<b>Diagnosis</b>	<b>Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension Dose (mL)</b>
Bursitis under heloma durum or heloma molle	0.25 to 0.5
under calcaneal spur	0.5
over hallux rigidus of digiti quinti varus	0.5
Tenosynovitis, periostitis of cuboid	0.5
Acute gouty arthritis	0.5 to 1

## **2.10 HOW SUPPLIED**

NDC 0517-0720-01:

Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension, 5 mL multiple dose vial; box of one. Inactive ingredients per mL: 7.1 mg dibasic sodium phosphate anhydrous; 3.4 mg monobasic sodium phosphate monohydrate; 0.1 mg edetate disodium; and 0.2 mg benzalkonium chloride as preservative.

### **SHAKE WELL BEFORE USING.**

**Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].**

**Protect from light.**

**Rx only**

Revised July 2018

**MCKESSON ALCOHOL PREP PAD- isopropyl alcohol swab**

### ***Drug Facts***

#### **Active ingredient**

Isopropyl Alcohol 70% v/v

## **Purpose**

First Aid Antiseptic

## **Use**

For preparation of the skin prior to an injection

## **Warnings**

- **For external use only**
- Flammable, keep away from fire or flame
- Do not use with electrocautery procedures
- Do not use in the eyes
- Do not apply to irritated skin
- Stop use if pain, irritation, redness, or swelling occurs, discontinue use and consult a physician.
- **Keep out from reach of children.** If swallowed, get medical help or contact a Poison Control Center right away.

## **Directions**

- Open packet
- Remove pad
- Apply topically as needed to cleanse intended area. Discard after single use.

## **Other information**

- Store at room temperature 59-86°F (15-30°C)
- Contents sterile in unopened, undamaged package

## **Inactive ingredients**

purified water

## **H-Paxin Injection System**

### **Contents:**

- 1 - 50mL 2% Lidocaine HCl (20mg/mL)
- 1 - 50mL .25 Bupivacaine HCl (2.5mg/mL)
- 1 - 5mL Betamethasone Sodium Phosphate and Betamethasone Acetate (6mg/mL)
- 1 - 3cc Syringe w/ 18-22 Gauge 1-1 1/2 in Needle (Draw)
- 1 - 22-27 Gauge 1-1 1/2 inch Needle (Administer)
- 1 - 3x3 Gauze Sponge Sterile Square

1 - Bandage 1x3 in

4 - Alcohol Prep Pads

Assembled and Distributed by IT3 Medical, LLC 190 E Stacy Road; STE 306-298 Allen, TX 75002-8734

For questions or comments: info@IT3-Medical.com, www.IT3-Medical.com

## PACKAGING-KIT LABEL

NDC 70529-051-01

Rx ONLY



# H-Paxin Injection System

### Contents:

- |   |  |
|---|--|
| 1 - 50mL 2% Lidocaine HCl (20mg/mL)                                       | 1- 3cc Syringe w/ 18-22 Gauge 1-1 1/2 in Needle (Draw) |
| 1 - 50mL .25% Bupivacaine HCl (2.5mg/mL)                                  | 1 - 22-27 Gauge 1-1 1/2 inch Needle (Administer)       |
| 1 - 5mL Betamethasone Sodium Phosphate and Betamethasone Acetate (6mg/mL) | 1 - 3x3 Gauze Sponge Sterile Square                    |
|   | 1 - Bandage 1x3 in                                     |
|   | 4 - Alcohol Prep Pads                                  |



Single use only



Caution, consult accompanying documents



Consult instructions for use

20°C  
68°F



Temperature limitations

25°C  
77°F

Storage: Store in a cool dry place at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F). See USP Controlled Room Temperature.



Lot/Expiration >

Lot : 111617  
Exp : 8-1-18

Assembled and Distributed by IT3 Medical, LLC 190 E Stacy Road; STE 306-298 Allen, TX 75002-8734  
For questions or comments: info@IT3-Medical.com, www.IT3-Medical.com  
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## PACKAGING-KIT COMPONENTS LABELING

AUROMEDICS

NDC 55150-249-50

# 0.25% Bupivacaine HCl Injection USP

125 mg per 50 mL  
(2.5 mg/mL)

Rx only

for INFILTRATION and NERVE BLOCK

Not for caudal, epidural, or spinal anesthesia

50 mL Multiple Dose Vial

**Sterile, Nonpyrogenic**

Each mL contains 2.5 mg bupivacaine hydrochloride USP (equivalent to 2.2 mg bupivacaine), with 1 mg methylparaben as preservative and sodium chloride to make isotonic, in Water for Injection. pH adjusted with sodium hydroxide or hydrochloric acid. **Usual Dosage:** See package insert.

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

Distributed by:

**AuroMedics Pharma LLC**

279 Princeton-Hightstown Rd.  
E. Windsor, NJ 08520

Made in India

P1418047

Code: TS/DRUGS/13/2010



NDC 0517-0720-01

# Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension, USP 30 mg/5 mL (6 mg/mL)

5 mL MULTIPLE DOSE VIAL

Sterile  
Rx Only

AMERICAN  
REGENT, INC.  
SHIRLEY, NY 11967

For intramuscular, intra-articular or soft tissue administration, intralesional, intrabursal, and intradermal use.

**NOT FOR INTRAVENOUS USE.**

Shake well before using. Protect from light. Store at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature).

Usual Dosage: See Package Insert.

Rev. 07/16 RN1072-01



NDC 68599-5804-1

# MCKESSON Alcohol Prep Pad

STERILE | SATURATED WITH  
70% v/v ISOPROPYL ALCOHOL

M  
MEDIUM

1.2" x 2.6"  
(3 cm x 6.5 cm)



DO NOT  
REUSE

MFR # 58-204

STAMP AREA

STAMP AREA

### Drug Facts

Active ingredient	Purpose
Isopropyl Alcohol 70% v/v .....	First Aid Antiseptic

**Use** For preparation of the skin prior to an injection

### Warnings

For external use only.

- Flammable, keep away from fire or flame
- Do not use with electrocautery procedures or in eyes
- Stop use if redness or irritation develops. If condition continues for more than 72 hours consult a physician

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

**Directions** Apply alcohol as needed to clean intended area. Discard after single use.

**Inactive ingredient** Purified Water

**Questions?** Call 1-800-777-4908

See Box for full Drug Facts Information. Not for individual sale.

Distributed By McKesson Medical-Surgical Inc.  
Richmond, VA 23228

Rev. 01 01/14 Made in China

## H-PAXIN

lidocaine hydrochloride, bupivacaine hydrochloride, betamethasone sodium phosphate and

betamethasone acetate kit

## Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:70529-051
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## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70529-051-01	1 in 1 PACKAGE; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)	08/01/2018	

## Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL, MULTI-DOSE	50 mL
Part 2	1 VIAL, MULTI-DOSE	50 mL
Part 3	1 VIAL, MULTI-DOSE	5 mL
Part 4	4 PACKET	4 mL

## Part 1 of 4

### LIDOCAINE HYDROCHLORIDE

lidocaine hydrochloride injection, solution

## Product Information

<b>Item Code (Source)</b>	NDC:0409-4277
<b>Route of Administration</b>	INFILTRATION, PERINEURAL

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LIDOCAINE HYDROCHLORIDE (UNII: V13007Z41A) (LIDOCAINE - UNII:98PI200987)	LIDOCAINE HYDROCHLORIDE ANHYDROUS	20 mg in 1 mL

## Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	6 mg in 1 mL
WATER (UNII: 059QF0KO0R)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
METHYLPARABEN (UNII: A2I8C7HI9T)	1 mg in 1 mL

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		50 mL in 1 VIAL, MULTI-DOSE; Type 0: Not a Combination Product		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA088327	06/15/2005	

## Part 2 of 4

### BUPIVACAINE HYDROCHLORIDE

bupivacaine hydrochloride injection, solution

## Product Information

Item Code (Source)	NDC:55150-249
Route of Administration	INFILTRATION, PERINEURAL

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
BUPIVACAINE HYDROCHLORIDE (UNII: 7TQO7W3VT8) (BUPIVACAINE - UNII:Y8335394RO)	BUPIVACAINE HYDROCHLORIDE ANHYDROUS	2.5 mg in 1 mL

## Inactive Ingredients

Ingredient Name	Strength
METHYLPARABEN (UNII: A2I8C7HI9T)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
WATER (UNII: 059QF0KO0R)	

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		50 mL in 1 VIAL, MULTI-DOSE; Type 0: Not a Combination Product		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA207183	05/13/2016	

## Part 3 of 4

# BETAMETHASONE SODIUM PHOSPHATE AND BETAMETHASONE ACETATE

betamethasone sodium phosphate and betamethasone acetate injection, suspension

## Product Information

Item Code (Source)	NDC:0517-0720
Route of Administration	INTRA-ARTICULAR, INTRALESIONAL, INTRAMUSCULAR

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>BETAMETHASONE ACETATE</b> (UNII: T105AO53L7) (BETAMETHASONE - UNII:9842X06Q6M)	BETAMETHASONE ACETATE	3 mg in 1 mL
<b>BETAMETHASONE SODIUM PHOSPHATE</b> (UNII: 7BK02SCL3W) (BETAMETHASONE - UNII:9842X06Q6M)	BETAMETHASONE	3 mg in 1 mL

## Inactive Ingredients

Ingredient Name	Strength
<b>SODIUM PHOSPHATE, DIBASIC, ANHYDROUS</b> (UNII: 22ADO53M6F)	7.1 mg in 1 mL
<b>SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE</b> (UNII: 593YOG76RN)	3.4 mg in 1 mL
<b>EDETATE DISODIUM</b> (UNII: 7FLD91C86K)	0.1 mg in 1 mL
<b>BENZALKONIUM CHLORIDE</b> (UNII: F5UM2KM3W7)	0.2 mg in 1 mL
<b>WATER</b> (UNII: 059QF0KO0R)	

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		5 mL in 1 VIAL, MULTI-DOSE; Type 0: Not a Combination Product		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090747	04/28/2010	

## Part 4 of 4

### MCKESSON ALCOHOL PREP PAD

isopropyl alcohol swab

#### Product Information

**Item Code (Source)** NDC:68599-5804

**Route of Administration** TOPICAL

#### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ISOPROPYL ALCOHOL (UNII: ND2M416302) (ISOPROPYL ALCOHOL - UNII:ND2M416302)	ISOPROPYL ALCOHOL	0.7 mL in 1 mL

#### Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	

#### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		1 mL in 1 PACKET; Type 0: Not a Combination Product		

#### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
OTC monograph not final	part333A	04/09/2010	

#### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA088327	08/01/2018	

**Labeler** - IT3 Medical LLC (079971231)