

# **MARLIDO 25 KIT- lidocaine hydrochloride, bupivacaine hydrochloride, povidone iodine**

**Asclemed USA, Inc.**

*Disclaimer: This drug has not been found by FDA to be safe and effective, and this labeling has not been approved by FDA. For further information about unapproved drugs, click here.*

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## **HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use BUPIVACAINE HYDROCHLORIDE INJECTION safely and effectively. See full prescribing information for BUPIVACAINE HYDROCHLORIDE INJECTION. BUPIVACAINE HYDROCHLORIDE injection, for infiltration, perineural, caudal, epidural, or retrobulbar use. Initial U.S. Approval: 1972**

### **WARNING: RISK OF CARDIAC ARREST WITH USE OF BUPIVACAINE HYDROCHLORIDE IN OBSTETRICAL ANESTHESIA**

*See full prescribing information for complete boxed warning.*

**There have been reports of cardiac arrest with difficult resuscitation or death during use of BUPIVACAINE HYDROCHLORIDE INJECTION for epidural anesthesia in obstetrical patients. In most cases, this has followed use of the 0.75% (7.5 mg/mL) 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% (7.5 mg/mL) concentration of BUPIVACAINE HYDROCHLORIDE INJECTION is not recommended for obstetrical anesthesia and should be reserved for surgical procedures where a high degree of muscle relaxation and prolonged effect are necessary ( 5.1).**

## **INDICATIONS AND USAGE**

Bupivacaine Hydrochloride Injection contains bupivacaine, an amide local anesthetic is indicated in adults for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures. For each type of block indicated to produce local or regional anesthesia or analgesia, specific concentrations and presentations are recommended. ( 1, 2.2)

### Limitations of Use

Not all blocks are indicated for use with Bupivacaine Hydrochloride Injection given clinically significant risks associated with use. ( 1, 2.2, 4, 5.1, 5.5, 5.7, 5.9)

## **DOSAGE AND ADMINISTRATION**

- Not for intrathecal use. ( 2.1)
- Avoid use of solutions containing antimicrobial preservatives (i.e., multiple-dose vials) for epidural or caudal anesthesia. ( 2.1)
- See full prescribing information for:
  - Recommended concentrations and dosages of Bupivacaine Hydrochloride according to type of block. ( 2.2)
  - Additional dosage and administration information pertaining to use in epidural anesthesia and use in ophthalmic surgery. ( 2.3, 2.6)

## **DOSAGE FORMS AND STRENGTHS**

Bupivacaine Hydrochloride injection is available in multiple concentrations. See full prescribing information for detailed description of each formulation. ( 3)

## **CONTRAINDICATIONS**

- Obstetrical paracervical block anesthesia. Its use in this technique has resulted in fetal bradycardia and death. ( 4)
- Intravenous regional anesthesia (Bier Block). ( 4)
- Known hypersensitivity to bupivacaine or to any local anesthetic agent of the amide-type or to other components of Bupivacaine Hydrochloride injection. ( 4)

## **WARNINGS AND PRECAUTIONS**

- Dose-Related Toxicity: Monitor cardiovascular and respiratory vital signs and patient's state of consciousness after injection of Bupivacaine Hydrochloride injection. ( 5.2)
- Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use. See full prescribing information for more detail on managing these risks. ( 5.3)
- Chondrolysis with Intra-Articular Infusion: Intra-articular infusions of local anesthetics including Bupivacaine Hydrochloride injection following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of chondrolysis in patients receiving such infusions. ( 5.5)
- Risk of Cardiac Arrest with Intravenous Regional Anesthesia Use (Bier Block): There have been reports of cardiac arrest and death during the use of bupivacaine for intravenous regional anesthesia (Bier Block). ( 5.7)
- Risk of Systemic Toxicities with Unintended Intravascular or Intrathecal Injection: Unintended intravascular or intrathecal injection may be associated with systemic toxicities, including CNS or cardiorespiratory depression and coma, progressing ultimately to respiratory arrest. Aspirate for blood or cerebrospinal fluid (where applicable) prior to each dose ( 5.9)

#### -----ADVERSE REACTIONS-----

Most common adverse reactions are related to the central nervous system and the cardiovascular system. ( 6)

**To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

#### -----DRUG INTERACTIONS-----

- Local Anesthetics: The toxic effects of local anesthetics are additive. Monitor for neurologic and cardiovascular effects when additional local anesthetics are administered. ( 7.1)
- Drugs Associated with Methemoglobinemia: Patients are at increased risk of developing methemoglobinemia when concurrently exposed to nitrates, nitrites, local anesthetics, antineoplastic agents, antibiotics, antimalarials, anticonvulsants, and other drugs. ( 7.5)
- Potent Inhalation Anesthetics: Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are used in patients during or following the administration of potent inhalation anesthetics. ( 7.6)

#### -----USE IN SPECIFIC POPULATIONS-----

- Pediatric Use: Administration of Bupivacaine hydrochloride injection in pediatric patients younger than 12 years is not recommended. ( 8.4)
- Geriatric Use: Patients 65 years and over, particularly those with hypertension, may be at increased risk for developing hypotension while undergoing anesthesia with Bupivacaine Hydrochloride injection. ( 8.5)
- Moderate to Severe Hepatic Impairment: Consider increased monitoring for bupivacaine systemic toxicity. ( 8.6)

**See 17 for PATIENT COUNSELING INFORMATION and PATIENT COUNSELING INFORMATION.**

**Revised: 7/2022**

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## ***Caudal and Lumbar Epidural Block***

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Do not use

When using this product do not

Stop use and ask a doctor if

Keep out of reach of children.

\* Sections or subsections omitted from the full prescribing information are not listed.

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## **FULL PRESCRIBING INFORMATION**

### **WARNING: RISK OF CARDIAC ARREST WITH USE OF BUPIVACAINE HYDROCHLORIDE IN 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% (7.5 mg/mL) 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% (7.5 mg/mL) concentration of Bupivacaine Hydrochloride is not recommended for obstetrical anesthesia and should be reserved for surgical procedures where a high degree of muscle relaxation and prolonged effect are necessary [see *Warnings and Precautions (5.1)*].

## **1 INDICATIONS AND USAGE**

Bupivacaine Hydrochloride injection is indicated in adults for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures. Specific concentrations and presentations of Bupivacaine Hydrochloride injection are recommended for each type of block indicated to produce local or regional anesthesia or analgesia [see *Dosage and Administration (2.2)*].

### Limitations of Use

Not all blocks are indicated for use with Bupivacaine Hydrochloride injection given clinically significant risks associated with use [see *Dosage and Administration (2.2)*, *Contraindications (4)*, *Warnings and Precautions (5.1, 5.5, 5.7, 5.9)*].

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Important Dosage and Administration Information**

- Bupivacaine Hydrochloride injection is not for intrathecal use.
- Discard unused portions of solution not containing preservatives, i.e., those supplied

in single-dose vials, following initial use.

- Visually inspect this product for particulate matter and discoloration prior to administration whenever solution and container permit. Bupivacaine Hydrochloride injection is a clear, colorless solution. Do not administer solutions which are discolored or contain particulate matter.
- Mixing or the prior or intercurrent use of any other local anesthetic with Bupivacaine Hydrochloride is not recommended because of insufficient data on the clinical use of such mixtures.

#### Administration Precautions

- Bupivacaine Hydrochloride injection is to be administered in carefully adjusted dosages by or under the supervision of experienced clinicians who are well versed in the diagnosis and management of dose-related toxicity and other acute emergencies which might arise from the block to be employed.
- Use Bupivacaine Hydrochloride injection only if the following are immediately available: oxygen, cardiopulmonary resuscitative equipment and drugs, and the personnel resources needed for proper management of toxic reactions and related emergencies [see *Warnings and Precautions (5.2)*, *Adverse Reactions (6)*, *Overdosage (10)*].
- The toxic effects of local anesthetics are additive. Monitor for neurologic and cardiovascular effects related to local anesthetic systemic toxicity when additional local anesthetics are administered with Bupivacaine Hydrochloride injection [see *Warnings and Precautions (5.2)*, *Drug Interactions (7.1)*, *Overdosage (10)*].
- Aspirate for blood or cerebrospinal fluid (where applicable) prior to injecting Bupivacaine Hydrochloride injection, both the initial dose and all subsequent doses, to avoid intravascular or intrathecal injection. However, a negative aspiration for blood or cerebrospinal fluid does not ensure against an intravascular or intrathecal injection [see *Warnings and Precautions (5.9)*].
- Avoid rapid injection of a large volume of Bupivacaine Hydrochloride injection and use fractional (incremental) doses when feasible.
- During major regional nerve blocks, such as those of the brachial plexus or lower extremity, the patient should have an indwelling intravenous catheter to assure adequate intravenous access. The lowest dosage of Bupivacaine Hydrochloride injection that results in effective anesthesia should be used to avoid high plasma levels and serious adverse reactions.
- Perform careful and constant monitoring of cardiovascular and respiratory (adequacy of oxygenation and ventilation) vital signs and the patient's level of consciousness after each local anesthetic injection.

## **2.2 Recommended Concentrations and Dosages of Bupivacaine Hydrochloride injection**

The dosage of Bupivacaine Hydrochloride injection 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. Administer the smallest dosage and concentration required to produce the desired result.

The types of block and recommended Bupivacaine Hydrochloride injection concentrations are shown in Table 1.

### **Table 1. Types of Block and Recommended Bupivacaine Hydrochloride**

## Injection Concentrations

Type of Block	Bupivacaine Hydrochloride injection		
	0.25% (2.5 mg/mL)	0.5% (5 mg/mL)	0.75% (7.5 mg/mL)*
Local infiltration	✓		
Peripheral nerve block	✓	✓	
Retrobulbar block			✓
Sympathetic block	✓		
Caudal block	✓	✓	
Lumbar epidural block	✓	✓	✓ (not for obstetrical anesthesia)
Epidural test dose			
Dental block			

\* Bupivacaine Hydrochloride injection 0.75% (7.5 mg/mL) is not recommended for nonobstetrical surgical procedures in pregnant patients.

✓ = indicated use [see *Warnings and Precautions (5.1)*].

At recommended dosages, Bupivacaine Hydrochloride injection produces complete sensory block, but the effect on motor function differs among the three concentrations. Table 2 provides information on the expected effect on motor function for the three concentrations.

**Table 2. Bupivacaine Hydrochloride injection Concentration vs. Motor Function**

Bupivacaine Hydrochloride injection Concentration	Motor Function
0.25% (2.5 mg/mL)	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% (5 mg/mL) or 0.75% (7.5 mg/mL) solutions.
0.5% (5 mg/mL)	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

0.75% (7.5 mg/mL)	abdominal operations requiring complete muscle relaxation, and for retrobulbar anesthesia. Not for obstetrical anesthesia.
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The duration of anesthesia with Bupivacaine Hydrochloride injection is such that for most indications, a single-dose is sufficient.

The maximum dosage limit within the recommended dosage range must be individualized in each case after evaluating the size and physical status of the patient, as well as the anticipated rate of systemic absorption from a particular injection site.

The dosages in Table 3 are recommended as a guide for use in the average adult. These doses may be repeated once every three hours. Do not exceed a total daily dosage of 400 mg in 24 hours. The duration of anesthetic effect may be prolonged by the addition of epinephrine.

**Table 3. Recommended Concentrations and Doses of Bupivacaine Hydrochloride injection in Adults**

Type of Block	Concentration of Bupivacaine Hydrochloride injection	Each Dose		Motor Block <sup>a</sup>
		mL	mg of Bupivacaine Hydrochloride injection	
Local infiltration	0.25% (2.5 mg/mL) <sup>b</sup>	Up to 70 (without epinephrine)	Up to 175 (without epinephrine)	—
Peripheral nerve block	0.5% (5 mg/mL) <sup>b</sup>	5-35 (without epinephrine)	25-175 (without epinephrine)	moderate to complete
	0.25% (2.5 mg/mL) <sup>b</sup>	5-70 (without epinephrine)	12.5-175 (without epinephrine)	moderate to complete
Retrobulbar block <i>[see Dosage and Administration (2.6)]</i>	0.75% (7.5 mg/mL)	2-4	15-30	complete
Sympathetic block	0.25% (2.5 mg/mL)	20-50	50-125	—
Caudal block	0.5% (5 mg/mL) <sup>b</sup>	15-30	75-150	moderate to complete
	0.25% (2.5 mg/mL) <sup>b</sup>	15-30	37.5-75	moderate
Lumbar epidural block <i>[see Dosage and Administration</i>	0.75% (7.5 mg/mL) <sup>c</sup>	10-20	75-150	complete
	0.5% (5 mg/mL) <sup>b</sup>	10-20	50-100	moderate to complete

(2.3)]	0.25% (2.5 mg/mL) <sup>b</sup>	10-20	25-50	partial to moderate
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- With continuous (intermittent) techniques, repeat doses increase the degree of motor block. The first repeat dose of 0.5% (5 mg/mL) may produce complete motor block. Intercostal nerve block with 0.25% (2.5 mg/mL) also may produce complete motor block for intra-thoracic and upper intra-abdominal surgery.
- Solutions with or without epinephrine (i.e., applies to Bupivacaine Hydrochloride injection)
- For single-dose use; not for intermittent epidural technique. Not for obstetrical anesthesia.

### 2.3 Use in Epidural Anesthesia

During epidural administration, administer Bupivacaine Hydrochloride injection, 0.5% (5 mg/mL) and 0.75% (7.5 mg/mL) solutions in incremental doses of 3 mL to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Administer injections slowly, with frequent aspirations before and during the injection to avoid intravascular injection. Perform syringe aspirations before and during each supplemental injection in continuous (intermittent) catheter techniques. In obstetrics, use ONLY the 0.5% (5 mg/mL) and 0.25% (2.5 mg/mL) concentrations of Bupivacaine Hydrochloride injection [see *Warnings and Precautions (5.1)*]; incremental doses of 3 mL to 5 mL of the 0.5% (5 mg/mL) 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 clinically contraindicated. Use only the single-dose vials for caudal or epidural anesthesia; avoid use of the multiple-dose vials for these procedures, which contain a preservative [see *Dosage and Administration (2.1), Warnings and Precautions (5.9)*].

### 2.6 Use in Ophthalmic Surgery

When Bupivacaine Hydrochloride injection 0.75% (7.5 mg/mL) 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 [see *Warnings and Precautions (5.15)*].

## 3 DOSAGE FORMS AND STRENGTHS

Bupivacaine hydrochloride injection, USP is a clear, colorless solution available as:

- 0.25% (25 mg/10 mL) (2.5 mg/mL) in single-dose vials.
- 0.25% (75 mg/30 mL) (2.5 mg/mL) in single-dose vials.
- 0.5% (50 mg/10 mL) (5 mg/mL) in single-dose vials.
- 0.5% (150 mg/30 mL) (5 mg/mL) in single-dose vials.
- 0.75% (75 mg/10 mL) (7.5 mg/mL) in single-dose vials.
- 0.75% (225 mg/30 mL) (7.5 mg/mL) in single-dose vials.

## 4 CONTRAINDICATIONS



Bupivacaine Hydrochloride injection is contraindicated in:

- obstetrical paracervical block anesthesia. Its use in this technique has resulted in fetal bradycardia and death.
- intravenous regional anesthesia (Bier Block) [see *Warnings and Precautions (5.7)*].
- patients with a known hypersensitivity to bupivacaine or to any local anesthetic agent of the amide-type or to other components of Bupivacaine Hydrochloride injection.

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Risk of Cardiac Arrest with Use of Bupivacaine Hydrochloride injection in Obstetrical Anesthesia**

There have been reports of cardiac arrest with difficult resuscitation or death during use of Bupivacaine Hydrochloride injection for epidural anesthesia in obstetrical patients. In most cases, this has followed use of the 0.75% (7.5 mg/mL) 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% (7.5 mg/mL) concentration of Bupivacaine Hydrochloride injection is not recommended for obstetrical anesthesia and should be reserved for surgical procedures where a high degree of muscle relaxation and prolonged effect are necessary.

### **5.2 Dose-Related Toxicity**

The safety and effectiveness of Bupivacaine Hydrochloride injection depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be performed after injection of Bupivacaine Hydrochloride injection solutions.

Possible early warning signs of central nervous system (CNS) toxicity are restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, CNS depression, or drowsiness. 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.

During major regional nerve blocks, such as those of the brachial plexus or lower extremity, the patient should have an indwelling intravenous catheter to assure adequate intravenous access. Use the lowest dosage of Bupivacaine Hydrochloride injection that results in effective anesthesia to avoid high plasma levels and serious adverse effects. Avoid rapid injection of a large volume of Bupivacaine Hydrochloride solution and administer fractional (incremental) doses when feasible.

Injection of repeated doses of Bupivacaine Hydrochloride injection 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.

### **5.3 Methemoglobinemia**

Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition [see *Drug Interactions (7.5)*]. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.

Signs of methemoglobinemia may occur immediately or may be delayed some hours after exposure and are characterized by a cyanotic skin discoloration and/or abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious CNS and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue Bupivacaine Hydrochloride injection and any other oxidizing agents. Depending on the severity of the signs and symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. A more severe clinical presentation may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

### **5.5 Chondrolysis with Intra-Articular Infusion**

Intra-articular infusions of local anesthetics including Bupivacaine Hydrochloride injection 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 associated with chondrolysis. 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 2<sup>nd</sup> 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.

### **5.7 Risk of Cardiac Arrest with Intravenous Regional Anesthesia Use (Bier Block)**

There have been reports of cardiac arrest and death during the use of bupivacaine for intravenous regional anesthesia (Bier Block). Information on safe dosages and techniques of administration of Bupivacaine Hydrochloride injection in this procedure is lacking. Therefore, Bupivacaine Hydrochloride injection is contraindicated for use with this technique [see *Contraindications (4)*].

### **5.9 Risk of Systemic Toxicities with Unintended Intravascular or Intrathecal Injection**

Unintended intravascular or intrathecal injection of Bupivacaine Hydrochloride injection may be associated with systemic toxicities, including CNS or cardiorespiratory depression and coma, progressing ultimately to respiratory arrest. Unintentional intrathecal injection during the intended performance of caudal or lumbar epidural block or nerve blocks near the vertebral column has resulted in underventilation or apnea ("Total or High Spinal"). A high spinal has been characterized by paralysis of the legs, loss of consciousness, respiratory paralysis, and bradycardia [see *Adverse Reactions*

(6)].

Aspirate for blood or cerebrospinal fluid (where applicable) before injecting Bupivacaine Hydrochloride injection, both the initial dose and all subsequent doses, to avoid intravascular or intrathecal injection. However, a negative aspiration for blood or cerebrospinal fluid does not ensure against an intravascular or intrathecal injection.

#### **5.10 Risk of Toxicity in Patients with Hepatic Impairment**

Because amide local anesthetics such as bupivacaine are metabolized by the liver, consider reduced dosing and increased monitoring for bupivacaine systemic toxicity in patients with moderate to severe hepatic impairment who are treated with Bupivacaine Hydrochloride injection, especially with repeat doses [see *Use in Specific Populations (8.6)*].

#### **5.11 Risk of Use in Patients with Impaired Cardiovascular Function**

Bupivacaine Hydrochloride injection should be given in reduced doses in patients with impaired cardiovascular function (e.g., hypotension, heartblock) because they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by Bupivacaine Hydrochloride injection. Monitor patients closely for blood pressure, heart rate, and ECG changes.

#### **5.14 Risk of Adverse Reactions with Use in Head and Neck Area**

Small doses of local anesthetics (e.g., Bupivacaine Hydrochloride injection) injected into the head and neck area, including retrobulbar, dental, and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care.

Confusion, convulsions, respiratory depression, and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. They may also be due to puncture of the dural sheath of the optic nerve during retrobulbar block with diffusion of any local anesthetic along the subdural space to the midbrain. Monitor circulation and respiration and constantly observe patients receiving Bupivacaine Hydrochloride injection blocks. Resuscitative equipment and drugs, and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded [see *Dosage and Administration (2.2)*].

#### **5.15 Risk of Respiratory Arrest with 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 (e.g., with Bupivacaine Hydrochloride injection), as with all other regional procedures, resuscitative equipment and drugs, and personnel to manage respiratory arrest or depression, convulsions, and cardiac stimulation or depression should be immediately available [see *Warnings and Precautions (5.14)*]. 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 (1)*] .

### **5.16 Risk of Inadvertent Trauma to Tongue, Lips, and Buccal Mucosa in Dental Applications**

Because of the long duration of anesthesia, when Bupivacaine Hydrochloride injection with epinephrine [0.5% (5 mg/mL) of bupivacaine] is used for dental injections, warn patients about the possibility of inadvertent trauma to tongue, lips, and buccal mucosa and advise them not to chew solid foods until sensation returns [see *Patient Counseling Information (17)*] .

## **6 ADVERSE REACTIONS**

The following clinically significant adverse reactions have been reported and described in the Warnings and Precautions section of the labeling:

- Cardiac Arrest in Obstetrical Anesthesia [see *Warnings and Precautions (5.1)*]
- Dose-Related Toxicity [see *Warnings and Precautions (5.2)*]
- Methemoglobinemia [see *Warnings and Precautions (5.3)*]
- Chondrolysis with Intra-Articular Infusion [see *Warnings and Precautions (5.5)*]
- Cardiac Arrest with Intravenous Regional Anesthesia Use [see *Contraindications (4), Warnings and Precautions (5.7)*]
- Systemic Toxicities with Unintended Intravascular or Intrathecal Injection [see *Warnings and Precautions (5.9)*]
- Respiratory Arrest Following Retrobulbar Block [see *Warnings and Precautions (5.15)*]

The following adverse reactions from voluntary reports or clinical studies have been reported with bupivacaine or bupivacaine and epinephrine. Because many of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions to Bupivacaine Hydrochloride injection 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 overdose, unintentional intravascular injection, or slow metabolic degradation.

The most commonly encountered acute adverse reactions that demand immediate counter-measures were related to the CNS and the cardiovascular system. These adverse reactions were generally dose-related and due to high plasma levels which may have resulted from overdose, 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 intrathecal 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) has resulted 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 have occurred. This has led to secondary cardiac arrest when untreated.

Nervous System Disorders: Adverse reactions were characterized by excitation and/or

depression of the central nervous system and included restlessness, anxiety, dizziness, tinnitus, blurred vision, tremors, convulsions, drowsiness, unconsciousness, respiratory arrest, nausea, vomiting, chills, pupillary constriction.

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

Neurologic effects following epidural or caudal anesthesia have included 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 had 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 have included persistent anesthesia, paresthesia, weakness, paralysis, all with slow, incomplete, or no recovery.

*Convulsions:* Incidence varied 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. 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.

Cardiac Disorders: High doses or unintentional intravascular injection have led 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 and Precautions (5.9)*] .

Immune System Disorders: Allergic-type reactions have occurred as a result of sensitivity to bupivacaine or to other formulation ingredients, such as the antimicrobial preservative methylparaben contained in multiple-dose vials or sulfites in epinephrine-containing solutions. These reactions were characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and severe hypotension. Cross sensitivity among members of the amide-type local anesthetic group has been reported.

## **7 DRUG INTERACTIONS**

### **7.1 Local Anesthetics**

The toxic effects of local anesthetics are additive. If coadministration of other local anesthetics with Bupivacaine Hydrochloride injection cannot be avoided, monitor patients for neurologic and cardiovascular effects related to local anesthetic systemic toxicity [*see Dosage and Administration (2.1), Warnings and Precautions (5.2)*] .

## 7.5 Drugs Associated with Methemoglobinemia

Patients who are administered Bupivacaine Hydrochloride injection are at increased risk of developing methemoglobinemia when concurrently exposed to following drugs, which could include other local anesthetics [see *Warnings and Precautions (5.3)*].

### Examples of Drugs Associated with Methemoglobinemia:

Class	Examples
Nitrates/Nitrites	nitric oxide, nitroglycerin, nitroprusside, nitrous oxide
Local anesthetics	articaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine
Antineoplastic agents	cyclophosphamide, flutamide, hydroxyurea, isofamide, rasburicase
Antibiotics	dapsone, nitrofurantoin, para-aminosalicylic acid, sulfonamides
Antimalarials	chloroquine, primaquine
Anticonvulsants	phenobarbital, phenytoin, sodium valproate
Other drugs	acetaminophen, metoclopramide, quinine, sulfasalazine

## 7.6 Potent Inhalation Anesthetics

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are used in patients during or following the administration of potent inhalation anesthetics.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Bupivacaine Hydrochloride injection is contraindicated for obstetrical paracervical block anesthesia. Its use in this technique has resulted in fetal bradycardia and death [see *Contraindications (4)*, *Warnings and Precautions (5.1)*].

There are no available data on use of Bupivacaine Hydrochloride injection in pregnant women to inform a drug-associated risk of adverse developmental outcomes.

In animal studies, embryo-fetal lethality was noted when bupivacaine was administered subcutaneously to pregnant rabbits during organogenesis at clinically relevant doses. Decreased pup survival was observed in a rat pre- and post-natal developmental study (dosing from implantation through weaning) at a dose level comparable to the daily maximum recommended human dose (MRHD) on a body surface area (BSA) basis. Based on animal data, advise pregnant women of the potential risks to a fetus (see *Data*).

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 (12.3)*]. 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 CNS, peripheral vascular tone, and cardiac function.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, inform the patient of the potential hazard to the fetus. The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

## Clinical Considerations

### *Maternal Adverse Reactions*

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

### *Labor or Delivery*

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.

## Data

### *Animal Data*

Bupivacaine hydrochloride produced developmental toxicity when administered subcutaneously to pregnant rats and rabbits at clinically relevant doses.

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 MRHD of 400 mg/day on a mg/m<sup>2</sup> 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 0.3 times the MRHD on a BSA basis.

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

## **8.2 Lactation**

### Risk Summary

Lactation studies have not been conducted with bupivacaine. 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.

Bupivacaine Hydrochloride injection should be administered to lactating women only if clearly indicated. Studies assessing the effects of Bupivacaine Hydrochloride injection in breastfed children have not been performed. Studies to assess the effect of Bupivacaine Hydrochloride injection on milk production or excretion have not been performed. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bupivacaine and any potential adverse effects on the breastfed child from bupivacaine or from the underlying maternal condition.

## **8.4 Pediatric Use**

Bupivacaine Hydrochloride injection is approved for use in adults. Administration of Bupivacaine Hydrochloride injection in pediatric patients younger than 12 years is not recommended.

Continuous infusions of bupivacaine in pediatric patients have been reported to result in high systemic levels of bupivacaine and seizures; high plasma levels may also be associated with cardiovascular abnormalities.

## **8.5 Geriatric Use**

Patients 65 years and over, particularly those with hypertension, may be at increased risk for developing hypotension while undergoing anesthesia with Bupivacaine Hydrochloride injection.

In clinical studies of bupivacaine, elderly patients reached the maximal spread of analgesia and maximal motor blockade more rapidly than younger adult patients.

Differences in various pharmacokinetic parameters have been observed between elderly and younger adult patients [see *Clinical Pharmacology (12.3)*].

This product is known to be substantially excreted by the kidney, and the risk of adverse 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. Elderly patients may require lower doses of Bupivacaine Hydrochloride injection.

## **8.6 Hepatic Impairment**

Amide-type local anesthetics, such as bupivacaine, are metabolized by the liver. Patients with severe hepatic impairment, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations, and potentially



local anesthetic systemic toxicity. Therefore, consider reduced dosing and increased monitoring for local anesthetic systemic toxicity in patients with moderate to severe hepatic impairment treated with Bupivacaine Hydrochloride injection, especially with repeat doses [see *Warnings and Precautions (5.10)*].

## **8.7 Renal Impairment**

Bupivacaine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with renal impairment. This should be considered when selecting the Bupivacaine Hydrochloride injection dosage [see *Use in Specific Populations (8.5)*].

## **10 OVERDOSAGE**

### Clinical Presentation

Acute emergencies from use of Bupivacaine Hydrochloride injection are generally related to high plasma levels encountered during therapeutic use or to unintended intrathecal injection [see *Warnings and Precautions (5.2, 5.9), Adverse Reactions (6)*].

If not treated immediately, convulsions with simultaneous hypoxia, hypercarbia, and acidosis plus myocardial depression from the direct effects of bupivacaine may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities, including apnea, may occur.

Hypoventilation or apnea due to unintentional intrathecal injection of Bupivacaine Hydrochloride injection 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.

### Management

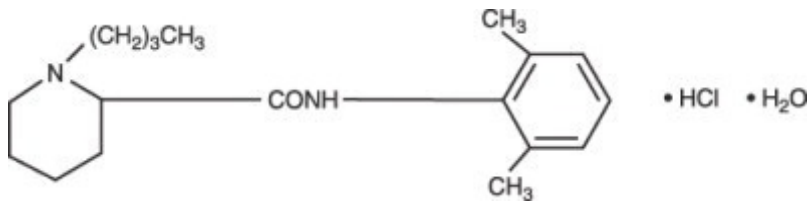
The first step in the management of systemic toxic reactions, as well as hypoventilation or apnea due to unintentional intrathecal injection of Bupivacaine Hydrochloride injection, consists of immediate attention to the establishment and maintenance of a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask. Endotracheal intubation, using 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.

If necessary, use drugs to manage the convulsions. A bolus intravenous dose of a benzodiazepine will counteract CNS stimulation related to Bupivacaine Hydrochloride injection. Immediately after the institution of ventilatory measures, evaluate the adequacy of the circulation. Supportive treatment of circulatory depression may require Advance Cardiac Life Support measures.

## **11 DESCRIPTION**

Bupivacaine hydrochloride injection, USP contains bupivacaine hydrochloride, an amide local anesthetic, as the active pharmaceutical ingredient. The route of administration for Bupivacaine Hydrochloride injection is by injection, for infiltration, perineural, caudal, epidural, or retrobulbar use.

Bupivacaine hydrochloride is 2-piperidinecarboxamide, 1-butyl- *N*-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate. It is a white crystalline powder that is freely soluble in 95 percent ethanol, soluble in water, and slightly soluble in chloroform or acetone. It has the following structural formula:



Bupivacaine hydrochloride injection, USP is a clear and colorless sterile isotonic solution. Each mL of single-dose vial contains 2.5 mg, 5 mg or 7.5 mg of bupivacaine hydrochloride (equivalent to 2.22 mg, 4.44 mg or 6.66 mg of bupivacaine, respectively), sodium chloride for isotonicity, sodium hydroxide or hydrochloric acid to adjust the pH between 4 and 6.5, in water for injection.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Bupivacaine blocks 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.

Epinephrine is a vasoconstrictor added to bupivacaine to slow absorption into the general circulation and thus prolong maintenance of an active tissue concentration.

### 12.2 Pharmacodynamics

Systemic absorption of bupivacaine produces effects on the cardiovascular system and 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. These cardiovascular changes are more likely to occur after unintended intravascular injection of bupivacaine [see *Warnings and Precautions (5.9)*].

Following systemic absorption, bupivacaine can produce CNS stimulation, CNS depression, or both. Apparent central stimulation is manifested as restlessness, tremors, and shivering, progressing to convulsions, followed by CNS depression and coma progressing ultimately to respiratory arrest. However, bupivacaine has a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited state.

The duration of local anesthesia after administration of Bupivacaine Hydrochloride injection is longer than that observed after administration of other commonly used

short-acting local anesthetics. There appears to be period of analgesia that persists after the resolution of the block and return of sensation.

The onset of action following dental injections is usually 2 to 10 minutes and may last up to 7 hours.

### **12.3 Pharmacokinetics**

Systemic plasma levels of bupivacaine following administration of Bupivacaine Hydrochloride injection do not correlate with local efficacy.

#### Absorption

The rate of systemic absorption of bupivacaine 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) 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 [see *Dosage and Administration (2)*].

After injection of Bupivacaine Hydrochloride for caudal, epidural, or peripheral nerve block, 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.

#### Distribution

Bupivacaine appears 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 bupivacaine 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, bupivacaine is 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 (Bupivacaine Hydrochloride Injection is not approved for intravenous use) 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.

#### Elimination

The half-life of bupivacaine in adults is 2.7 hours.

#### *Metabolism*

Amide-type local anesthetics such as bupivacaine are metabolized primarily in the liver via conjugation with glucuronic acid. Pipecoloxyline is the major metabolite of bupivacaine. The elimination of drug from tissue distribution depends largely upon the

availability of binding sites in the circulation to carry it to the liver where it is metabolized.

### *Excretion*

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.

### Specific Populations

#### *Geriatric Patients*

Elderly patients exhibited higher peak plasma concentrations than younger patients following administration of Bupivacaine Hydrochloride Injection. The total plasma clearance was decreased in these patients [see *Use in Specific Populations (8.5)*].

#### *Patients with Hepatic Impairment*

Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic disease. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics [see *Use in Specific Populations (8.6)*].

#### *Patients with Renal Impairment*

Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of renal disease, factors affecting urinary pH, and renal blood flow [see *Use in Specific Populations (8.5, 8.7)*].

## **13 NONCLINICAL TOXICOLOGY**

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

#### Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of bupivacaine hydrochloride have not been conducted.

#### Mutagenesis

The mutagenic potential of bupivacaine hydrochloride has not been determined.

#### Impairment of Fertility

The effect of bupivacaine on fertility has not been determined.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

Bupivacaine hydrochloride injection, USP —Solutions of bupivacaine hydrochloride injection, USP may be autoclaved. Autoclave at 15-pound pressure, 121 °C (250 °F) for 15 minutes. Protect from light. This product is clear and colorless. Do not use the solution if it is discolored or if it contains a precipitate.

<b>NDC No.</b>	<b>Container</b>	<b>Fill</b>	<b>Quantity</b>
----------------	------------------	-------------	-----------------

	0.25% — Contains 2.5 mg bupivacaine hydrochloride per mL.		
0143-9330-10	Single Dose Vial	10 mL	Cartons of 10
0143-9333-10	Single Dose Vial	30 mL	Cartons of 10
	0.5% — Contains 5 mg bupivacaine hydrochloride per mL.		
0143-9331-10	Single Dose Vial	10 mL	Cartons of 10
0143-9334-10	Single Dose Vial	30 mL	Cartons of 10
	0.75% — Contains 7.5 mg bupivacaine hydrochloride per mL.		
0143-9332-10	Single Dose Vial	10 mL	Cartons of 10
0143-9335-10	Single Dose Vial	30 mL	Cartons of 10

For single-dose vials: Discard unused portion.

## 17 PATIENT COUNSELING INFORMATION

### Allergic-Type Reactions

Assess if the patient has had allergic-type reactions to amide-type local anesthetics [see *Contraindications (4)*].

### Temporary Loss of Sensation and Motor Activity After Caudal or Epidural Anesthesia

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.

### Instructions After Dental Injection of Bupivacaine Hydrochloride injection

Advise patients receiving dental injections of Bupivacaine Hydrochloride injection not to chew solid foods or to test the anesthetized area by biting or probing until anesthesia has worn off (up to 7 hours) [see *Warnings and Precautions (5.16)*].

### Methemoglobinemia

Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; lightheadedness; or fatigue [see *Warnings and Precautions (5.3)*].

### **Manufactured by:**

HIKMA FARMACÊUTICA (PORTUGAL), S.A.

Estrada do Rio da Mó, no 8, 8A e 8B - Fervença, 2705 - 906 Terrugem SNT, PORTUGAL

### **Distributed by:**

Hikma Pharmaceuticals USA Inc.

Berkeley Heights, NJ 07922

Revised: February 2021

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## Lidocaine Hydrochloride Injection, USP

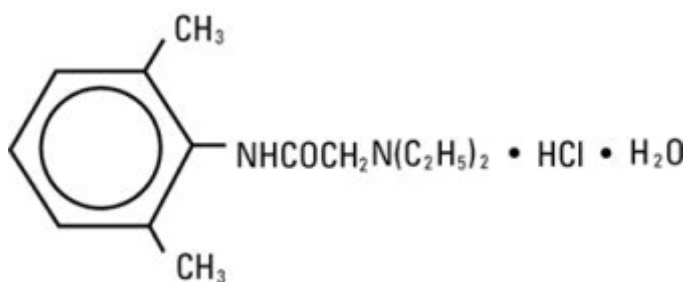
For Infiltration and Nerve Block

Rx only

### DESCRIPTION

Lidocaine hydrochloride injection, USP is sterile, nonpyrogenic, aqueous solution that contains a local anesthetic agent and is administered parenterally by injection. See **INDICATIONS AND USAGE** section for specific uses.

Lidocaine hydrochloride injection, USP contains lidocaine hydrochloride, which is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-, monohydrochloride and has the molecular weight 270.8. Lidocaine hydrochloride ( $C_{14}H_{22}N_2O \cdot HCl$ ) has the following structural formula:



Lidocaine hydrochloride injection, USP is a sterile, nonpyrogenic, isotonic solution containing sodium chloride. The pH of the solution is adjusted to approximately 6.5 (5.0 to 7.0) with sodium hydroxide and/or hydrochloric acid.

### CLINICAL PHARMACOLOGY

#### *Mechanism of Action*

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

#### *Hemodynamics*

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

#### *Pharmacokinetics and Metabolism*

Information derived from diverse formulations, concentrations and usages reveals that lidocaine is completely absorbed following parenteral administration, its rate of absorption depending, for example, upon various factors such as the site of

administration and the presence or absence of a vasoconstrictor agent. Except for intravascular administration, the highest blood levels are obtained following intercostal nerve block and the lowest after subcutaneous administration.

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

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

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

The elimination half-life of lidocaine following an intravenous bolus injection is typically 1.5 to 2 hours. Because of the rapid rate at which lidocaine is metabolized, any condition that affects liver function may alter lidocaine kinetics. The half-life may be prolonged two-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.

Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lidocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6 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 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 hydrochloride 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.

### ***Methemoglobinemia***

Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.

Signs of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by a cyanotic skin discoloration and/or abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue lidocaine hydrochloride and any other oxidizing agents. Depending on the severity of the signs and symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. A more severe clinical presentation may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been postmarketing 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 2<sup>nd</sup> 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.

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 hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride injection should be used with caution in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations. Lidocaine hydrochloride injection 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 hydrochloride 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 hydrochloride.

### ***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 injection 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.

Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; lightheadedness; or fatigue.

### ***Clinically Significant Drug Interactions***

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

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

Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

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

### ***Drug/Laboratory Test Interactions***

The intramuscular injection of lidocaine hydrochloride 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 hydrochloride.

Patients who are administered local anesthetics are at increased risk of developing methemoglobinemia when concurrently exposed to the following drugs, which could include other local anesthetics:

### **Examples of Drugs Associated with Methemoglobinemia:**

<b>Class</b>	<b>Examples</b>
Nitrates/Nitrites	nitric oxide, nitroglycerin, nitroprusside, nitrous oxide
Local anesthetics	articaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine
Antineoplastic agents	cyclophosphamide, flutamide, hydroxyurea, ifosfamide, rasburicase
Antibiotics	dapsone, nitrofurantoin, para-aminosalicylic acid, sulfonamides
Antimalarials	chloroquine, primaquine
Anticonvulsants	Phenobarbital, phenytoin, sodium valproate
Other drugs	acetaminophen, metoclopramide, quinine, sulfasalazine

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

Studies of lidocaine hydrochloride 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 hydrochloride. 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 hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride 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 to local anesthetic agents. 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 hydrochloride 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 overdose with lidocaine hydrochloride.

The oral LD<sub>50</sub> of lidocaine hydrochloride 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 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 hydrochloride injection 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 hydrochloride is quite low, caution should be exercised when employing large volumes and concentrations, since the incidence of side effects is directly proportional to the total dose of local anesthetic agent injected.

### ***Epidural Anesthesia***

For epidural anesthesia, only the following dosage forms of lidocaine hydrochloride injection are recommended:

1% without epinephrine 5 mL ampules

2% without epinephrine 2 mL ampules

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 hydrochloride should be administered at least 5 minutes prior to injecting the total volume required for a lumbar or caudal epidural block. The test dose should be repeated if the patient is moved in a manner that may have displaced the catheter. Epinephrine, if contained in the test dose (10 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**

### ***Adults***

For normal healthy adults, 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 hydrochloride 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. Do not use if solution is discolored or contains a precipitate.

**Table 1: Recommended Dosages**

Procedure	Lidocaine Hydrochloride Injection (without epinephrine)		
	Conc (%)	Vol (mL)	Total Dose (mg)
Infiltration			
Percutaneous	0.5 or 1	1 to 60	5 to 300
Intravenous regional	0.5	10 to 60	50 to 300
Peripheral Nerve Blocks, e.g.,			
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
Sympathetic Nerve Blocks, e.g.,			
Cervical (stellate ganglion)	1	5	50
Lumbar	1	5 to 10	50 to 100
Central Neural Blocks			
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.

## **HOW SUPPLIED**

Lidocaine Hydrochloride Injection USP, is supplied as follows:

Lidocaine Hydrochloride Injection USP, 1% (10 mg/mL)

2 mL Ampules in a Carton of 10 NDC 55150-158-72

### **Sterile, Nonpyrogenic**

Discard unused portion.

**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

Manufactured by:

**Eugia Pharma Specialities Limited**  
Hyderabad - 500032  
India

Revised: October 2021

## **Povidone-Iodine Swabsticks**

### **Active Ingredient Purpose**

Povidone Iodine 10% w/v (9.85% w/w) Antiseptic

### **Purpose:**

Purpose:

- First aid antiseptic to help prevent skin infection in minor cuts, scrapes and burns.
- For preparation of the skin prior to surgery.

- Helps reduce bacteria that can potentially cause skin infections.

**Warnings:**

- **FOR EXTERNAL USE ONLY**

**Do not use:**

- As a first aid antiseptic for more than 1 week.
- In the eyes.
- Over large areas of the body.

**Ask a doctor before use if you have:**

- Deep puncture wounds
- Animal bites
- Serious burns

**Stop Use:**

- If irritation and redness develop
- If condition persists for more than 72 hours, consult a physician.

**Keep Out Of Reach Of Children**

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

**Directions Povidone iodine:**

Tear at notch, remove applicator, use only once.

**As a first aid antiseptic**

- clean affected area
- apply 1 to 3 times daily
- may be covered with a sterile bandage, if bandaged let dry.

**For preoperative patient skin preparation**

- clean area
- apply to operative site prior to surgery using the applicator

**Other information:**

Store at room temperature.

Avoid excessive heat

For use as an

- first aid antiseptic
- pre-operative skin preparation

**Inactive Ingredients**

Inactive ingredients: Citric acid, glycerin, polysorbate 80, sodium citrate USP, sodium phosphate dibasic, water

**Povidone-Iodine Swabsticks****Active ingredient**

Isopropyl Alcohol 70% v/v

**Purpose**

Antiseptic

**Uses**

For first aid to decrease germs in

- minor cuts
- scrapes
- burns

For preparation of the skin prior to injection

**Warnings**

**For external use only**

**Flammable - keep away from fire or flame**

**Do not use**

with electrocautery procedures

**When using this product do not**

- get into eyes
- apply over large areas of the body
- in case of deep or puncture wounds, animal bites or serious burns consult a doctor

**Stop use and ask a doctor if**

- condition persists or gets worse or lasts for more than 72 hours
- do not use longer than 1 week unless directed by a doctor

**Keep out of reach of children.**

If swallowed, get medical help or contact a Poison Control Center right away.

**Directions**

- apply to skin as needed
- discard after single use

**Other information**

Protect from freezing and avoid excessive heat

**Inactive ingredient**

Water

**PRINCIPAL DISPLAY PANEL**

**NDC: 76420-735-01**

**Rx Only**

**Marlido-25™**

**Kit Contains**

1 Bupivacaine HCl 0.25% Single Dose Vial (10mL)

1 Lidocaine HCl Injection, USP 1% Ampule (2mL)

1 Povidone-Iodine Swabsticks (3 Swabs)

2 Isopropyl Alcohol 70% Prep Pads

1 Pair Nitrile Powder Free Sterile Gloves (M)

1 Drape

1 Adhesive Bandage

5 Non Sterile 4x4 Gauze

Needles and Syringes Not Included

1 Dose

Single Use Only

Distributed by:

Enovachem™

PHARMACEUTICALS

Torrance, CA 90501

# Marlido-25<sup>TM</sup>

## Kit Contains

1	Bupivacaine HCl 0.25% Single Dose Vial (10mL)
1	Lidocaine HCl Injection, USP 1% Ampule (2mL)
1	Povidone-Iodine Swabsticks (3 Swabs)
2	Isopropyl Alcohol 70% Prep Pads
1	Pair Nitrile Powder Free Sterile Gloves (M)
1	Drape
1	Adhesive Bandage
5	Non Sterile 4x4 Gauze

Needles and Syringes Not Included

1 Dose  
Single Use Only

Distributed by



## MARLIDO 25 KIT

lidocaine hydrochloride, bupivacaine hydrochloride, povidine iodine kit

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:76420-735
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### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:76420-735-01	1 in 1 CARTON; Type 1: Convenience Kit of Co-Package	05/23/2016	

### Quantity of Parts

Part #	Package Quantity	Total Product Quantity
<b>Part 1</b>	1 AMPULE	2 mL
<b>Part 2</b>	1 VIAL, SINGLE-DOSE	10 mL
<b>Part 3</b>	1 PACKET	0.9 mL
<b>Part 4</b>	2 POUCH	10 mL

## Part 1 of 4

### LIDOCAINE HYDROCHLORIDE

lidocaine hydrochloride injection, solution

#### Product Information

Item Code (Source)	NDC:55150-158
Route of Administration	INFILTRATION, PERINEURAL, INTRACAUDAL, EPIDURAL

#### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LIDOCAINE HYDROCHLORIDE (UNII: V13007Z41A) (LIDOCAINE - UNII:98PI200987)	LIDOCAINE HYDROCHLORIDE ANHYDROUS	10 mg in 1 mL

#### Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	7 mg in 1 mL
WATER (UNII: 059QF0KO0R)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	

#### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55150-158-72	10 in 1 CARTON		
1		2 mL in 1 AMPULE; Type 0: Not a Combination Product		

#### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203040	03/14/2013	

## Part 2 of 4

### BUPIVACAINE HYDROCHLORIDE

bupivacaine hydrochloride injection, solution



**Product Information**

<b>Item Code (Source)</b>	NDC:0143-9330
<b>Route of Administration</b>	EPIDURAL, INFILTRATION

**Active Ingredient/Active Moiety**

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

**Inactive Ingredients**

<b>Ingredient Name</b>	<b>Strength</b>
<b>SODIUM CHLORIDE</b> (UNII: 451W47IQ8X)	
<b>SODIUM HYDROXIDE</b> (UNII: 55X04QC32I)	
<b>HYDROCHLORIC ACID</b> (UNII: QTT17582CB)	
<b>WATER</b> (UNII: 059QF0K00R)	

**Packaging**

<b>#</b>	<b>Item Code</b>	<b>Package Description</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
1	NDC:0143-9330-10	10 in 1 CARTON		
1	NDC:0143-9330-01	10 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

**Marketing Information**

<b>Marketing Category</b>	<b>Application Number or Monograph Citation</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
ANDA	ANDA204842	02/11/2021	

**Part 3 of 4****POVIDINE IODINE**

povidine iodine swab

**Product Information**

<b>Item Code (Source)</b>	NDC:67777-419
<b>Route of Administration</b>	TOPICAL

**Active Ingredient/Active Moiety**

<b>Ingredient Name</b>	<b>Basis of Strength</b>	<b>Strength</b>
<b>POVIDONE-IODINE</b> (UNII: 85H0HZU99M) (IODINE - UNII:9679TC07X4)	IODINE	10 mg in 1 mL

## Inactive Ingredients

Ingredient Name	Strength
GLYCERIN (UNII: PDC6A3C00X)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
SODIUM CITRATE (UNII: 1Q73Q2JULR)	
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS (UNII: 22ADO53M6F)	
CITRIC ACID ACETATE (UNII: DSO12WL7AU)	
WATER (UNII: 059QF0KO0R)	

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67777-419-02	0.9 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 final	part333C	09/13/2016	

## Part 4 of 4

### ISOPROPYL ALCOHOL

isopropyl alcohol swab

## Product Information

Route of Administration TOPICAL

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ISOPROPYL ALCOHOL (UNII: ND2M416302) (ISOPROPYL ALCOHOL - UNII:ND2M416302)	ISOPROPYL ALCOHOL	70 mL in 100 mL

## Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		5 mL in 1 POUCH; Type 0: Not a Combination Product		
<b>Marketing Information</b>				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
OTC monograph not final	part333A	01/01/2007		
<b>Marketing Information</b>				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
unapproved drug other		09/08/2009		

**Labeler** - Asclemed USA, Inc. (059888437)

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Asclemed USA, Inc.