

MARDEX 25 KIT- dexamethasone sodium phosphate, bupivacaine hydrochloride, povidine iodine
Asclemed USA, Inc.

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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 INJECTION 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. 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. 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, 5.4, 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, 5.4)
- Three mL of Bupivacaine Hydrochloride and Epinephrine Injection without antimicrobial preservative (0.5% bupivacaine with 1:200,000 epinephrine) is recommended for use as a test dose prior to caudal and lumbar epidural blocks when clinical conditions permit. (2.4)
- See full prescribing information for:
 - Recommended concentrations and dosages of Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine Injection according to type of block. (2.2)
 - Additional dosage and administration information pertaining to use in epidural anesthesia, test dose for caudal and lumbar epidural blocks, use in dentistry, and use in ophthalmic surgery. (2.3, 2.4, 2.5,

-----DOSAGE FORMS AND STRENGTHS-----

Bupivacaine Hydrochloride Injection, USP are 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/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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)
- Allergic-Type Reactions to Sulfites in Bupivacaine Hydrochloride and Epinephrine Injection: Bupivacaine Hydrochloride and Epinephrine Injection contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. (5.8)
- 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 and consider using a test dose of Bupivacaine Hydrochloride and Epinephrine Injection. (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 Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or 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)
- Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: Administration of Bupivacaine Hydrochloride and Epinephrine Injection to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Concurrent use of these agents should generally be avoided. (5.6, 7.2)
- Ergot-Type Oxytocic Drugs: Concurrent administration of Bupivacaine Hydrochloride and Epinephrine Injection and ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accidents. (5.6, 7.3)
- Nonselective Beta-Adrenergic Antagonists: Administration of Bupivacaine Hydrochloride and Epinephrine Injection (containing a vasoconstrictor) in patients receiving nonselective beta-adrenergic antagonists may cause severe hypertension and bradycardia. Concurrent use of these agents should generally be avoided. (5.6, 7.4)
- 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. (5.13, 7.6)

----- **USE IN SPECIFIC POPULATIONS** -----

- **Pediatric Use:** Administration of Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine Injection. (8.5)
- **Moderate to Severe Hepatic Impairment:** Consider increased monitoring for bupivacaine systemic toxicity. (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION

WARNING: 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 [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, 5.4, 5.5, 5.7, 5.9)] .

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

- Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine Injection is not for intrathecal use.
- Avoid use of Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine Injection solutions containing antimicrobial preservatives (i.e., multiple-dose vials) for epidural or caudal anesthesia [see Warnings and Precautions (5.4)] .
- 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/Bupivacaine Hydrochloride and Epinephrine Injection are clear, colorless solutions. 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 Injection/Bupivacaine Hydrochloride and Epinephrine Injection is not

recommended because of insufficient data on the clinical use of such mixtures.

Administration Precautions

- Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine Injection are 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/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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.
- Use Bupivacaine Hydrochloride and Epinephrine Injection in carefully restricted quantities in areas of the body supplied by end arteries or having otherwise compromised blood supply such as digits, nose, external ear, or penis [see *Warnings and Precautions (5.12)*].

2.2 Recommended Concentrations and Dosages of Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine Injection

The dosage of Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine Injection concentrations are shown in Table 1.

Table 1. Types of Block and Recommended Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine Injection Concentrations

Type of Block	Bupivacaine Hydrochloride			Bupivacaine Hydrochloride and Epinephrine	
	0.25% (2.5 mg/mL)	0.5% (5 mg/mL)	0.75% (7.5 mg/mL) *	0.25% (2.5 mg/mL)	0.5% (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					✓

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

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

† Avoid use of multiple-dose vials of Bupivacaine Hydrochloride Injection and Bupivacaine Hydrochloride and Epinephrine Injection for caudal or epidural anesthesia [see Warnings and Precautions (5.4)].

At recommended dosages, Bupivacaine Hydrochloride/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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

(2.5 mg/mL)	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% (7.5 mg/mL) †	Produces complete motor block. Most useful for epidural block in abdominal operations requiring complete muscle relaxation, and for retrobulbar anesthesia. Not for obstetrical anesthesia.

* These products include Bupivacaine Hydrochloride Injection and Bupivacaine Hydrochloride and Epinephrine Injection [the epinephrine concentration (1:200,000) is not included in the table].

† These are only Bupivacaine Hydrochloride Injection products [there is no 0.75% (7.5 mg/mL) concentration for Bupivacaine Hydrochloride and Epinephrine Injection].

The duration of anesthesia with Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine Injection in Adults

Type of Block	Concentration of Bupivacaine Hydrochloride Injection	Each Dose		Motor Block *
		mL	mg of Bupivacaine Hydrochloride Injection	
Local infiltration	0.25% (2.5 mg/mL) †	Up to 70 (without epinephrine)	Up to 175 (without epinephrine)	—
		Up to 90 (with epinephrine)	Up to 225 (with epinephrine)	
Peripheral	0.5% (5 mg/mL) †	5-35 (without epinephrine)	25-175 (without epinephrine)	moderate to complete
		5-45 (with epinephrine)	25-225 (with epinephrine)	

nerve block	0.25% (2.5 mg/mL) †	5-70 (without epinephrine)	12.5-175 (without epinephrine)	moderate to complete
		5-90 (with epinephrine)	12.5-225 (with epinephrine)	
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 <i>[see Dosage and Administration (2.4)]</i>	0.5% (5 mg/mL) †	15-30	75-150	moderate to complete
	0.25% (2.5 mg/mL) †	15-30	37.5-75	moderate
Lumbar epidural block <i>[see Dosage and Administration (2.3)]</i>	0.75% (7.5 mg/mL) ‡	10-20	75-150	complete
	0.5% (5 mg/mL) †	10-20	50-100	moderate to complete
	0.25% (2.5 mg/mL) †	10-20	25-50	partial to moderate
Epidural test dose <i>[see Dosage and Administration (2.4)]</i>	0.5% (5 mg/mL) with epinephrine	2-3	10-15 (10-15 micrograms epinephrine)	—
Dental <i>[see Dosage and Administration (2.5)]</i>	0.5% (5 mg/mL) with epinephrine	1.8-3.6 per site	9-18 per site	—

* 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 and Bupivacaine Hydrochloride and Epinephrine Injection). The Bupivacaine Hydrochloride and Epinephrine Injection products include epinephrine (1:200,000).

‡ For single-dose use; not for intermittent epidural technique. Not for obstetrical anesthesia.

2.3 Use in Epidural Anesthesia

During the administration of epidural anesthesia, it is recommended that a test dose of Bupivacaine Hydrochloride and Epinephrine Injection without antimicrobial preservative

(0.5% bupivacaine with 1:200,000 epinephrine) be administered initially and the effects monitored before the full dose is given. When using a "continuous" catheter technique, test doses should be given prior to both the initial and all supplemental doses, because a catheter in the epidural space can migrate into a blood vessel or through the dura [see *Dosage and Administration (2.4)*].

During epidural administration, administer Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine Injection, 0.5% (5 mg/mL) and Bupivacaine Hydrochloride Injection 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/Bupivacaine Hydrochloride and Epinephrine 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, 2.4)*, *Warnings and Precautions (5.4, 5.9)*].

2.4 Test Dose for Caudal and Lumbar Epidural Blocks

Three mL of Bupivacaine Hydrochloride and Epinephrine Injection without antimicrobial preservative (0.5% bupivacaine with 1:200,000 epinephrine) is recommended for use as a test dose prior to caudal and lumbar epidural blocks when clinical conditions permit. This test dose may serve as a warning of unintended intravascular or intrathecal injection. Closely monitor for early clinical signs of toxicity following each test dose [see *Warnings and Precautions (5.9)*]. Allot adequate time for onset of spinal block to detect possible intrathecal injection. An intravascular or intrathecal injection is still possible even if results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, high spinal, or cardiovascular effects from the epinephrine [see *Warnings and Precautions (5.2, 5.9)*, *Overdosage (10)*].

2.5 Use in Dentistry

Bupivacaine Hydrochloride and Epinephrine Injection 0.5% (5 mg/mL) is recommended for infiltration and block injection in the maxillary and mandibular area when a longer duration of local anesthesia is desired, such as for procedures generally associated with significant postoperative pain. The average dose of 1.8 mL (9 mg) per injection site will usually suffice; an occasional second dose of 1.8 mL (9 mg) may be used if necessary to produce adequate anesthesia after allowing 2 to 10 minutes for block onset [see *Clinical Pharmacology (12.2)*]. Use the lowest effective dose and allow time between injections; it is recommended that the total dose for all injection sites, spread out over a single dental sitting, not exceed 90 mg for a healthy adult patient (ten 1.8 mL injections of 0.5% (5 mg/mL) Bupivacaine Hydrochloride and Epinephrine Injection). Inject slowly and with frequent aspirations.

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 teartop vials.
- 0.25% (75 mg/30 mL) (2.5 mg/mL) in single-dose teartop vials.
- 0.25% (125 mg/50 mL) (2.5 mg/mL) in multiple-dose flip-top vials.

- 0.5% (50 mg/10 mL) (5 mg/mL) in single-dose teartop vials.
- 0.5% (150 mg/30 mL) (5 mg/mL) in single-dose teartop vials.
- 0.5% (250 mg/50 mL) (5 mg/mL) in multiple-dose flip-top vials.

- 0.75% (75 mg/10 mL) (7.5 mg/mL) in single-dose teartop vials.
- 0.75% (225 mg/30 mL) (7.5 mg/mL) in single-dose teartop vials.

4 CONTRAINDICATIONS

Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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 Injection/Bupivacaine Hydrochloride and Epinephrine Injection solution and administer fractional (incremental) doses when feasible.

Injection of repeated doses of Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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.

5.4 Antimicrobial Preservatives in Multiple-Dose Vials

Avoid use of Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine Injection solutions containing antimicrobial preservatives, i.e., those supplied in multiple-dose vials, for epidural or caudal anesthesia because safety has not been established with such use.

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 2nd month after surgery. Currently, there is no effective treatment for chondrolysis; patients who experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

5.6 Risk of Adverse Reactions Due to Drug Interactions with Bupivacaine Hydrochloride and Epinephrine Injection

Risk of Severe, Persistent Hypertension Due to Drug Interactions Between Bupivacaine Hydrochloride and Epinephrine Injection and Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Administration of Bupivacaine Hydrochloride and Epinephrine Injection (containing a vasoconstrictor) in patients receiving monoamine oxidase inhibitors (MAOI), or tricyclic antidepressants may result in severe, prolonged hypertension. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful monitoring of the patient's hemodynamic status is essential [see *Drug Interactions (7.2)*].

Risk of Severe, Persistent Hypertension or Cerebrovascular Accidents Due to Drug Interactions Between Bupivacaine Hydrochloride and Epinephrine Injection and Ergot-Type Oxytocic Drugs

Concurrent administration of Bupivacaine Hydrochloride and Epinephrine Injection and ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accidents. Avoid use of Bupivacaine Hydrochloride and Epinephrine Injection concomitantly with ergot-type oxytocic drugs [see *Drug Interactions (7.3)*].

Risk of Hypertension and Bradycardia Due to Drug Interactions Between Bupivacaine Hydrochloride and Epinephrine Injection and Nonselective Beta-Adrenergic Antagonists

Administration of Bupivacaine Hydrochloride and Epinephrine Injection (containing a vasoconstrictor) in patients receiving nonselective beta-adrenergic antagonists may cause severe hypertension and bradycardia. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful monitoring of the patient's blood pressure and heart rate is essential [see *Drug Interactions (7.4)*].

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/Bupivacaine Hydrochloride and Epinephrine Injection is contraindicated for use with this technique [see *Contraindications (4)*].

5.8 Allergic-Type Reactions to Sulfites in Bupivacaine Hydrochloride and Epinephrine Injection

Bupivacaine Hydrochloride and Epinephrine Injection contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people. Bupivacaine Hydrochloride Injection without epinephrine does not contain sodium metabisulfite.

5.9 Risk of Systemic Toxicities with Unintended Intravascular or Intrathecal Injection

Unintended intravascular or intrathecal injection of Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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.

Use of Test Dose with Epidural Anesthesia

To serve as a warning of unintended intravascular or intrathecal injection, 3 mL of Bupivacaine Hydrochloride and Epinephrine Injection without antimicrobial preservative (0.5% bupivacaine with 1:200,000 epinephrine) may be used as a test dose prior to administration of the full dose in caudal and lumbar epidural blocks [see *Dosage and Administration (2.4)*]. Three mL of Bupivacaine Hydrochloride and Epinephrine Injection without antimicrobial preservative (0.5% bupivacaine with 1:200,000 epinephrine) contains 15 mg bupivacaine and 15 mcg epinephrine. An intravascular or intrathecal injection is still possible even if results of the test dose are negative.

Signs/symptoms of unintended intravascular or intrathecal injection of the test dose of Bupivacaine Hydrochloride and Epinephrine Injection and monitoring recommendations are described below.

- Unintended *intravascular* injection: Likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and/or systolic blood pressure, circumoral pallor, palpitations, and nervousness in the unsedated patient. The sedated patient may exhibit only a pulse rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, the heart rate should be monitored for increases. Patients on beta-blockers may not manifest changes in heart rate, but blood pressure monitoring can detect a transient rise in systolic blood pressure.
- Unintended *intrathecal* injection: Evidenced within a few minutes by signs of spinal block (e.g., decreased sensation of the buttocks, paresis of the legs, or, in the sedated patient, absent knee jerk).

The test dose itself may produce a systemic toxic reaction, high spinal or epinephrine-induced cardiovascular effects [see *Overdosage (10)*].

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 Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine Injection. Monitor patients closely for blood pressure, heart rate, and ECG changes.

5.12 Risk of Ischemic Injury or Necrosis in Body Areas with Limited Blood Supply

Use Bupivacaine Hydrochloride and Epinephrine Injection in carefully restricted quantities in areas of the body supplied by end arteries or having otherwise compromised blood supply such as digits, nose, external ear, or penis. Patients with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result.

5.13 Risk of Cardiac Arrhythmias with Concomitant Use of Potent Inhalation Anesthetics

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine (e.g., Bupivacaine Hydrochloride and Epinephrine Injection) are used in patients during or following the administration of potent inhalation anesthetics [see *Drug Interactions (7.6)*]. In deciding whether to concurrently use Bupivacaine Hydrochloride and Epinephrine Injection with potent inhalation anesthetics in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

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/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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 and Epinephrine Injection [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)*]

- Severe, Persistent Hypertension, Cerebrovascular Accidents, and Bradycardia Due to Drug Interactions [see *Warnings and Precautions (5.6)*]
- Cardiac Arrest with Intravenous Regional Anesthesia Use [see *Contraindications (4), Warnings and Precautions (5.7)*]
- Allergic-Type Reactions [see *Warnings and Precautions (5.8)*]
- 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/Bupivacaine Hydrochloride and Epinephrine 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 overdosage, 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 overdosage, rapid absorption from the injection site, diminished tolerance, or from unintentional intravascular injection of the local anesthetic solution. In addition to systemic dose-related toxicity, unintentional 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 [see *Warnings and Precautions (5.8)*].

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/Bupivacaine Hydrochloride and Epinephrine 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)*].

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

The administration Bupivacaine Hydrochloride and Epinephrine Injection to patients receiving monoamine oxidase inhibitors, or tricyclic antidepressants may produce severe, prolonged hypertension. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful monitoring of the patient's hemodynamic status is essential [see *Warnings and Precautions (5.6)*].

7.3 Ergot-Type Oxytocic Drugs

Concurrent administration of Bupivacaine Hydrochloride and Epinephrine Injection and ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accidents. Avoid use of Bupivacaine Hydrochloride and Epinephrine concomitantly with ergot-type oxytocic drugs [see *Warnings and Precautions (5.6)*].

7.4 Nonselective Beta-Adrenergic Antagonists

Administration of Bupivacaine Hydrochloride and Epinephrine Injection (containing a vasoconstrictor) in patients receiving nonselective beta-adrenergic antagonists may cause severe hypertension and bradycardia. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful monitoring of the patient's blood pressure and heart rate is essential [see *Warnings and Precautions (5.6)*].

7.5 Drugs Associated with Methemoglobinemia

Patients who are administered Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine 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 (e.g., Bupivacaine Hydrochloride and Epinephrine Injection) are used in patients during or following the administration of potent inhalation anesthetics [see *Warnings and Precautions (5.13)*].

7.7 Phenothiazines and Butyrophenones

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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^2 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/Bupivacaine Hydrochloride and Epinephrine Injection should be administered to lactating women only if clearly indicated. Studies assessing the effects of Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine Injection in breastfed children have not been performed. Studies to assess the effect of Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine Injection is approved for use in adults. Administration of Bupivacaine Hydrochloride

Injection/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine Injection dosage [see *Use in Specific Populations (8.5)*].

10 OVERDOSAGE

Clinical Presentation

Acute emergencies from use of Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine 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/Bupivacaine Hydrochloride and Epinephrine 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

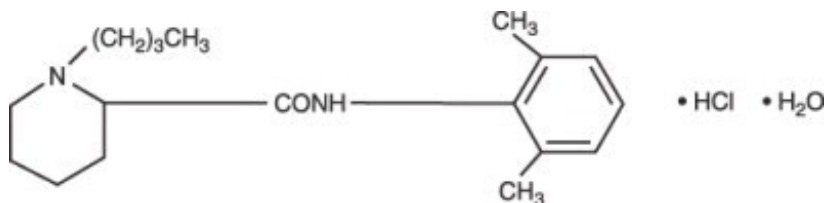
The first step in the management of systemic toxic reactions, as well as hypoventilation or apnea due to unintentional intrathecal injection of Bupivacaine Hydrochloride Injection/Bupivacaine Hydrochloride and Epinephrine Injection, consists of immediate attention to the establishment and maintenance 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 contains bupivacaine hydrochloride, an amide local anesthetic, as the active pharmaceutical ingredient. The route of administration for Bupivacaine Hydrochloride Injection (without epinephrine) is by injection, for infiltration, perineural, caudal, epidural, or retrobulbar use. Multiple-dose vials contain methylparaben [see *Warnings and Precautions (5.4)*].

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.

For the multiple-dose vials, each mL also contains 1 mg methylparaben as preservative.

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. The duration of anesthetic effect is prolonged by the addition of epinephrine 1:200,000.

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 Injection 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. Pipecoloxylidine 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 that do not contain epinephrine may be autoclaved. Autoclave at 15-pound pressure, 121 °C (250 °F) for 15 minutes. This product is clear and colorless. Do not use the solution if it is discolored or if it contains a precipitate.

Unit of Sale	Concentration
NDC 0409-1159-01 Tray of 25 single-dose teartop vials	0.25% 25 mg/10 mL (2.5 mg/mL)
NDC 0409-1159-02 Tray of 25 single-dose teartop vials	0.25% 75 mg/30 mL (2.5 mg/mL)
NDC 0409-1160-01 Tray of 25 multiple-dose flip-top vials	0.25% 125 mg/50 mL (2.5 mg/mL)
NDC 0409-1163-01 Tray of 25 multiple-dose flip-top vials	0.5% 250 mg/50 mL (5 mg/mL)

NDC 0409-1162-01 Tray of 25 single-dose teartop vials	0.5% 50 mg/10 mL (5 mg/mL)
NDC 0409-1162-02 Tray of 25 single-dose teartop vials	0.5% 150 mg/30 mL (5 mg/mL)
NDC 0409-1165-01 Tray of 25 single-dose teartop vials	0.75% 75 mg/10 mL (7.5 mg/mL)
NDC 0409-1165-02 Tray of 25 single-dose teartop vials	0.75% 225 mg/30 mL (7.5 mg/mL)

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 or to other formulation ingredients, such as the antimicrobial preservative methylparaben contained in multiple-dose vials or sulfites in epinephrine-containing solutions [see *Contraindications (4)*, *Warnings and Precautions (5.8)*, *Adverse Reactions (6)*].

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)*].

This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

Distributed by Hospira, Inc., Lake Forest, IL 60045 USA

LAB-1176-5.0

Dexamethasone Sodium Phosphate Injection, USP

For Intravenous or Intramuscular Use Only

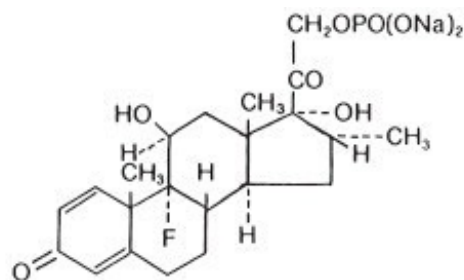
Rx only

DESCRIPTION

Dexamethasone Sodium Phosphate Injection, USP, is a water-soluble inorganic ester of dexamethasone which produces a rapid response even when injected intramuscularly.

Dexamethasone Sodium Phosphate, USP chemically is Pregna-1,4-diene-3,20-dione, 9-fluoro- 11,17-dihydroxy-16-methyl-21-(phosphonoxy)-, disodium salt, (11 β , 16 α).

It occurs as a white to creamy white powder, is exceedingly hygroscopic, is soluble in water and its solutions have a pH between 7.0 and 8.5. It has the following structural formula:



$C_{22}H_{28}FNa_2O_8P$

M.W. 516.41

Each mL of Dexamethasone Sodium Phosphate Injection, USP (**Preservative Free**) contains dexamethasone sodium phosphate, USP equivalent to 10 mg dexamethasone phosphate; 24.75 mg sodium citrate, dihydrate; and Water for Injection, q.s. pH adjusted with citric acid or sodium hydroxide, if necessary. pH: 7.0 to 8.5.

CLINICAL PHARMACOLOGY

Dexamethasone sodium phosphate injection has a rapid onset but short duration of action when compared with less soluble preparations. Because of this, it is suitable for the treatment of acute disorders responsive to adrenocortical steroid therapy.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs, including dexamethasone, are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

At equipotent anti-inflammatory doses, dexamethasone almost completely lacks the sodium-retaining property of hydrocortisone and closely related derivatives of hydrocortisone.

INDICATIONS AND USAGE

By intravenous or intramuscular injection when oral therapy is not feasible:

1. Endocrine Disorders

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance).

Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used).

Preoperatively, and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful.

Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected.

Congenital adrenal hyperplasia

Nonsuppurative thyroiditis

Hypercalcemia associated with cancer

2. Rheumatic Disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

Post-traumatic osteoarthritis

Synovitis of osteoarthritis

Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy).

Acute and subacute bursitis

Epicondylitis

Acute nonspecific tenosynovitis

Acute gouty arthritis

Psoriatic arthritis

Ankylosing spondylitis

3. Collagen Diseases

During an exacerbation or as maintenance therapy in selected cases of:

Systemic lupus erythematosus

Acute rheumatic carditis

4. Dermatologic Diseases

Pemphigus

Severe erythema multiforme (Stevens-Johnson syndrome)

Exfoliative dermatitis

Bullous dermatitis herpetiformis

Severe seborrheic dermatitis

Severe psoriasis

Mycosis fungoides

5. Allergic States

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:

Bronchial asthma

Contact dermatitis

Atopic dermatitis

Serum sickness

Seasonal or perennial allergic rhinitis

Drug hypersensitivity reactions

Urticarial transfusion reactions

Acute noninfectious laryngeal edema (epinephrine is the drug of first choice).

6. Ophthalmic Diseases

Severe acute and chronic allergic and inflammatory processes involving the eye, such as:

Herpes zoster ophthalmicus

Iritis, iridocyclitis

Chorioretinitis

Diffuse posterior uveitis and choroiditis

Optic neuritis

Sympathetic ophthalmia

Anterior segment inflammation

Allergic conjunctivitis

Keratitis

Allergic corneal marginal ulcers

7. Gastrointestinal Diseases

To tide the patient over a critical period of the disease in:

Ulcerative colitis (systemic therapy)

Regional enteritis (systemic therapy)

8. Respiratory Diseases

Symptomatic sarcoidosis

Berylliosis

Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy.

Loeffler's syndrome not manageable by other means.

Aspiration pneumonitis

9. Hematologic Disorders

Acquired (autoimmune) hemolytic anemia.

Idiopathic thrombocytopenic purpura in adults

(IV only; IM administration is contraindicated).

Secondary thrombocytopenia in adults

Erythroblastopenia (RBC anemia)

Congenital (erythroid) hypoplastic anemia

10. Neoplastic Diseases

For palliative management of:

Leukemias and lymphomas in adults

Acute leukemia of childhood

11. Edematous States

To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

12. Miscellaneous

Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.

Trichinosis with neurologic or myocardial involvement.

13. Diagnostic testing of adrenocortical hyperfunction.

14. Cerebral Edema associated with primary or metastatic brain tumor, craniotomy, or head injury. Use in cerebral edema is not a substitute for careful neurosurgical evaluation

and definitive management such as neurosurgery or other specific therapy.

CONTRAINDICATIONS

Systemic fungal infections (see **WARNINGS** regarding amphotericin B).

Hypersensitivity to any component of this product (see **WARNINGS**) .

WARNINGS

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug. Anaphylactoid and hypersensitivity reactions have been reported for dexamethasone sodium phosphate injection (see **ADVERSE REACTIONS**).

Corticosteroids may exacerbate systemic fungal infections and, therefore, should not be used in the presence of such infections unless they are needed to control drug reactions due to amphotericin B. Moreover, there have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive failure.

In patients on corticosteroid therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstated. If the patient is receiving steroids already, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Moreover, corticosteroids may affect the nitroblue-tetrazolium test for bacterial infection and produce false negative results.

In cerebral malaria, a double-blind trial has shown that the use of corticosteroids is associated with prolongation of coma and a higher incidence of pneumonia and gastrointestinal bleeding.

Corticosteroids may activate latent amebiasis. Therefore, it is recommended that latent or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

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

Administration of live virus vaccines, including smallpox, is contraindicated in individuals receiving immunosuppressive doses of corticosteroids. If inactivated viral or bacterial vaccines are administered to individuals receiving immunosuppressive doses of corticosteroids, the expected serum antibody response may not be obtained. However, immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Patients who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. The risk of developing a disseminated infection varies among individuals and can be related to the dose, route and duration of corticosteroid administration as well as to the underlying disease. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered. If exposed to measles, prophylaxis with immune globulin (IG) may be indicated. (See the respective package inserts for VZIG and IG for complete prescribing information).

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

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

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

Serious Neurologic Adverse Reactions with Epidural Administration

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

Usage in Pregnancy

Since adequate human reproduction studies have not been done with corticosteroids, use of these drugs in pregnancy or in women of childbearing potential requires that the anticipated benefits be weighed against the possible hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. Mothers taking pharmacologic doses of corticosteroids should be advised not to nurse.

PRECAUTIONS

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

Following prolonged therapy, withdrawal of corticosteroids may result in symptoms of

the corticosteroid withdrawal syndrome including fever, myalgia, arthralgia, and malaise. This may occur in patients even without evidence of adrenal insufficiency.

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

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

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

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

Aspirin should be used with caution in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving large doses of corticosteroids may be minimal or absent. Fat embolism has been reported as a possible complication of hypercortisonism.

When large doses are given, some authorities advise that antacids be administered between meals to help prevent peptic ulcer.

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

Phenytoin, phenobarbital, ephedrine, and rifampin may enhance the metabolic clearance of corticosteroids resulting in decreased blood levels and lessened physiologic activity, thus requiring adjustment in corticosteroid dosage. These interactions may interfere with dexamethasone suppression tests which should be interpreted with caution during administration of these drugs.

False negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.

The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time because of reports that corticosteroids have altered the response to these anticoagulants. Studies have shown that the usual effect produced by adding corticosteroids is inhibition of response to coumarins, although there have been some conflicting reports of potentiation not substantiated by studies.

When corticosteroids are administered concomitantly with potassium-depleting diuretics, patients should be observed closely for development of hypokalemia.

The slower rate of absorption by intramuscular administration should be recognized.

Information for Patients

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

Pediatric Use

Growth and development of infants and children patients on prolonged corticosteroid therapy should be carefully followed.

ADVERSE REACTIONS

Fluid and electrolyte disturbances:

Sodium retention

Fluid retention

Congestive heart failure in susceptible patients

Potassium loss

Hypokalemic alkalosis

Hypertension

Musculoskeletal:

Muscle weakness

Steroid myopathy

Loss of muscle mass

Osteoporosis

Vertebral compression fractures

Aseptic necrosis of femoral and humeral heads

Tendon rupture

Pathologic fracture of long bones

Gastrointestinal:

Peptic ulcer with possible subsequent perforation and hemorrhage

Perforation of the small and large bowel; particularly in patients with inflammatory bowel disease

Pancreatitis

Abdominal distention

Ulcerative esophagitis

Dermatologic:

Impaired wound healing

Thin fragile skin

Petechiae and ecchymoses

Erythema

Increased sweating

May suppress reactions to skin tests

Burning or tingling, especially in the perineal area (after IV injection)

Other cutaneous reactions, such as allergic dermatitis, urticaria, angioneurotic edema

Neurologic:

Convulsions

Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment

Vertigo

Headache

Psychic disturbances

Endocrine:

Menstrual irregularities

Development of cushingoid state

Suppression of growth in pediatric patients

Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness

Decreased carbohydrate tolerance

Manifestations of latent diabetes mellitus

Increased requirements for insulin or oral hypoglycemic agents in diabetics

Hirsutism

Ophthalmic:

Posterior subcapsular cataracts

Increased intraocular pressure

Glaucoma

Exophthalmos

Retinopathy of prematurity

Metabolic:

Negative nitrogen balance due to protein catabolism

Cardiovascular:

Myocardial rupture following recent myocardial infarction (see **WARNINGS**)

Hypertrophic cardiomyopathy in low birth weight infants

Other:

Anaphylactoid or hypersensitivity reactions

Thromboembolism

Weight gain

Increased appetite

Nausea

Malaise

Hiccups

The following *additional* adverse reactions are related to parenteral corticosteroid therapy:

Hyperpigmentation or hypopigmentation

Subcutaneous and cutaneous atrophy

Sterile abscess

Charcot-like arthropathy

OVERDOSAGE

Reports of acute toxicity and/or death following overdosage of glucocorticoids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic.

The oral LD₅₀ of dexamethasone in female mice was 6.5 g/kg. The intravenous LD₅₀ of dexamethasone sodium phosphate in female mice was 794 mg/kg.

DOSAGE AND ADMINISTRATION

Dexamethasone sodium phosphate injection, 10 mg/mL– *For intravenous and intramuscular injection only.*

Dexamethasone sodium phosphate injection can be given directly from the vial, or it can be added to Sodium Chloride Injection or Dextrose Injection and administered by intravenous drip.

Solutions used for intravenous administration or further dilution of this product should be preservative free when used in the neonate, especially the premature infant.

When it is mixed with an infusion solution, sterile precautions should be observed. Since infusion solutions generally do not contain preservatives, mixtures should be used within 24 hours.

DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENT.

Intravenous and Intramuscular Injection

The initial dosage of dexamethasone sodium phosphate injection varies from 0.5 to 9 mg a day depending on the disease being treated. In less severe diseases doses lower than 0.5 mg may suffice, while in severe diseases doses higher than 9 mg may be required.

The initial dosage should be maintained or adjusted until the patient's response is satisfactory. If a satisfactory clinical response does not occur after a reasonable period of time, discontinue dexamethasone sodium phosphate injection and transfer the patient to other therapy.

After a favorable initial response, the proper maintenance dosage should be determined by decreasing the initial dosage in small amounts to the lowest dosage that maintains an adequate clinical response.

Patients should be observed closely for signs that might require dosage adjustment, including changes in clinical status resulting from remissions or exacerbations of the disease, individual drug responsiveness, and the effect of stress (e.g., surgery, infection, trauma). During stress it may be necessary to increase dosage temporarily.

If the drug is to be stopped after more than a few days of treatment, it usually should be withdrawn gradually.

When the intravenous route of administration is used, dosage usually should be the same as the oral dosage. In certain overwhelming, acute, life-threatening situations, however, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages. The slower rate of absorption by intramuscular administration should be recognized.

Shock

There is a tendency in current medical practice to use high (pharmacologic) doses of corticosteroids for the treatment of unresponsive shock. The following dosages of dexamethasone sodium phosphate injection have been suggested by various authors:

Author	Dosage
Cavanagh ¹	3 mg/kg of body weight per 24 hours by constant intravenous infusion after an initial intravenous injection of 20 mg
Dietzman ²	2 to 6 mg/kg of body weight as a single intravenous injection
Frank ³	40 mg initially followed by repeat intravenous injection every 4 to 6 hours while shock persists
Oaks ⁴	40 mg initially followed by repeat intravenous injection every 2 to 6 hours while shock persists
Schumer ⁵	1 mg/kg of body weight as a single intravenous injection

Administration of high dose corticosteroid therapy should be continued only until the patient's condition has stabilized and usually not longer than 48 to 72 hours.

Although adverse reactions associated with high dose, short-term corticosteroid therapy are uncommon, peptic ulceration may occur.

Cerebral Edema

Dexamethasone sodium phosphate injection is generally administered initially in a dosage of 10 mg intravenously followed by four mg every six hours intramuscularly until the symptoms of cerebral edema subside. Response is usually noted within 12 to 24 hours and dosage may be reduced after two to four days and gradually discontinued over a period of five to seven days. For palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy with 2 mg two or three times a day may be effective.

Acute Allergic Disorders

In acute, self-limited allergic disorders or acute exacerbations of chronic allergic disorders, the following dosage schedule combining parenteral and oral therapy is suggested:

Dexamethasone sodium phosphate injection, *first day*, 4 or 8 mg intramuscularly.

Dexamethasone tablets, 0.75 mg: *second and third days*, 4 tablets in two divided doses each day; *fourth day*, 2 tablets in two divided doses; *fifth and sixth days*, 1 tablet each day; *seventh day*, no treatment; *eighth day*, follow-up visit.

This schedule is designed to ensure adequate therapy during acute episodes, while minimizing the risk of overdosage in chronic cases.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever the solution and container permit.

HOW SUPPLIED

Dexamethasone Sodium Phosphate Injection, USP (**Preservative Free**) equivalent to 10 mg dexamethasone phosphate, is supplied in a single dose vial as follows:

Product No.	NDC No.	Strength	Vial Size
500601	63323-506-01	10 mg per mL	1 mL vial, packaged in twenty-fives.

This container closure is not made with natural rubber latex.

Storage

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Sensitive to heat. Do not autoclave.

Protect from freezing.

Protect from light.

Single dose vials-Store in container until time of use. Discard unused portion.

Multiple dose vials-Store in container until contents are used.

REFERENCES

1. Cavanagh, D.; Singh, K.B.: Endotoxin shock in pregnancy and abortion, in: "Corticosteroids in the Treatment of Shock", Schumer, W.; Nyhus, L.M., Editors, Urbana, University of Illinois Press, 1970, pp. 86-96.
2. Dietzman, R.H.; Ersek, R.A.; Bloch, J.M.; Lilleheir, R.C.: High-output, low-resistance gram-negative septic shock in man, *Angiology* 20: 691-700, Dec. 1969.
3. Frank, E.: Clinical observations in shock and management (in: Shields, T.F., ed.: Symposium on current concepts and management of shock), *J. Maine Med. Ass.* 59: 195-200, Oct. 1968.
4. Oaks, W. W.; Cohen, H.E.: Endotoxin shock in the geriatric patient, *Geriat.* 22: 120-130, Mar. 1967.
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45955E

Revised: May 2014

Povidone-Iodine Swabsticks

Active Ingredient

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

Purpose

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

Isopropyl Alcohol 70% Prep Pads

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: 76420-810-01****Rx Only****Mardex-25™****Kit Contains**

- 1 Bupivacaine HCl 0.25% Single Dose Vial (10mL)
- 1 Dexamethasone Sodium Phosphate Inj., USP 10mg/mL (1mL)
- 1 Povidone-Iodine Swabsticks (3 Swabs)
- 3 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

Mardex-25TM

Kit Contains

1	Bupivacaine HCl 0.25% Single Dose Vial (10mL)
1	Dexamethasone Sodium Phosphate Inj., USP 10mg/mL (1mL)
1	Povidone-Iodine Swabsticks (3 Swabs)
3	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



MARDEX 25 KIT

dexamethasone sodium phosphate, bupivacaine hydrochloride, povidine iodine kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:76420-810
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Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:76420-810-01	1 in 1 CARTON; Type 1: Convenience Kit of Co-Package	08/21/2014	

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL	1 mL
Part 2	1 VIAL, SINGLE-DOSE	10 mL
Part 3	1 PACKET	0.9 mL

Part 1 of 4**DEXAMETHASONE SODIUM PHOSPHATE**

dexamethasone sodium phosphate injection, solution

Product Information

Item Code (Source)	NDC:63323-506
Route of Administration	INTRAMUSCULAR, INTRAVENOUS

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DEXAMETHASONE SODIUM PHOSPHATE (UNII: AI9376Y64P) (DEXAMETHASONE - UNII: 7S5I7G3JQL)	DEXAMETHASONE PHOSPHATE	10 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM CITRATE (UNII: 1Q73Q2JULR)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63323-506-01	25 in 1 TRAY		
1		1 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040491	05/29/2003	

Part 2 of 4**BUPIVACAINE HYDROCHLORIDE**

bupivacaine hydrochloride injection, solution

Product Information

Item Code (Source)	NDC:0409-1159
Route of Administration	EPIDURAL, INFILTRATION, PERINEURAL

Active Ingredient/Active Moiety

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

Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
WATER (UNII: 059QF0KOOR)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0409-1159-18	10 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA070583	05/06/2005	

Part 3 of 4

POVIDINE IODINE

povidine iodine swab

Product Information

Item Code (Source)	NDC:67777-419
Route of Administration	TOPICAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
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POVIDONE-IODINE (UNII: 85H0HZU99M) (IODINE - UNII:9679TC07X4)	IODINE	10 mg in 1 mL
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Inactive Ingredients

Ingredient Name	Strength
GLYCERIN (UNII: PDC6A3C0OX)	
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
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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		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
OTC monograph not final	part333A	01/01/2007	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		08/21/2014	

Labeler - Asclemed USA, Inc. (059888437)

Revised: 12/2022

Asclemed USA, Inc.