

**MLK F4-C- bupivacaine hydrochloride, lidocaine hydrochloride, triamcinolone acetonide, iohexol, isopropyl alcohol, chlorhexidine gluconate  
Asclemed USA, Inc.**

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

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use BUPIVACAINE HYDROCHLORIDE INJECTION safely and effectively. See full prescribing information for BUPIVACAINE HYDROCHLORIDE INJECTION.**

**BUPIVACAINE HYDROCHLORIDE injection, for infiltration, perineural, caudal, epidural, or retrobulbar use**

**Initial U.S. Approval: 1972**

**WARNING: RISK OF CARDIAC ARREST WITH USE OF BUPIVACAINE HYDROCHLORIDE 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, 2.6)

----- **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](http://www.fda.gov/medwatch).**

## DRUG INTERACTIONS

- Local Anesthetics: The toxic effects of local anesthetics are additive. Monitor for neurologic and cardiovascular effects when additional local anesthetics are administered. ( 7.1)
- 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, PATIENT COUNSELING INFORMATION and PATIENT COUNSELING INFORMATION.**

**Revised: 7/2024**

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Do not use

When using this product do not

Stop use and ask a doctor if

Keep out of reach of children.

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

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## FULL PRESCRIBING INFORMATION

### **WARNING: RISK OF CARDIAC ARREST WITH USE OF BUPIVACAINE HYDROCHLORIDE 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%	When used for caudal, epidural, or peripheral nerve block, produces incomplete motor block. Should be used for operations in which muscle relaxation is not



0.25% (2.5 mg/mL) *	important, or when another means of providing muscle relaxation is used concurrently. Onset of action may be slower than with the 0.5% (5 mg/mL) or 0.75% (7.5 mg/mL) solutions.
0.5% (5 mg/mL) *	Provides motor blockade for caudal, epidural, or nerve block, but muscle relaxation may be inadequate for operations in which complete muscle relaxation is essential.
0.75% (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 [see Dosage and Administration (2.6)]	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 [see Dosage and Administration (2.4)]	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 [see Dosage and Administration (2.3)]	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 [see Dosage and Administration (2.4)]	0.5% (5 mg/mL) with epinephrine	2-3	10-15 (10-15 micrograms epinephrine)	—
Dental [see Dosage and Administration (2.5)]	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 fliptop 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 fliptop 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 2<sup>nd</sup> month after surgery. Currently, there is no effective treatment for chondrolysis; patients who experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

## 5.6 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  $\text{mg}/\text{m}^2\text{BSA}$  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

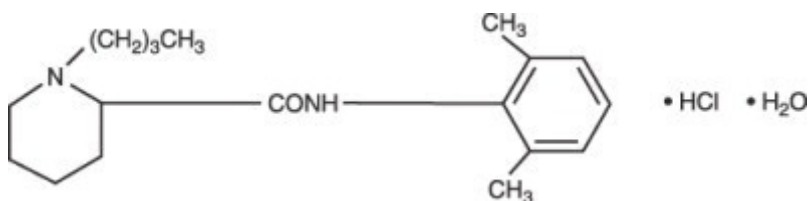
initial administration of oxygen by mask if difficulty is encountered in the maintenance of a patent airway, or if prolonged ventilatory support (assisted or controlled) is indicated.

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. Pipecoloxyline is the major metabolite of bupivacaine. The elimination of drug from tissue distribution depends largely upon the availability of binding sites in the circulation to carry it to the liver where it is metabolized.

#### *Excretion*

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

#### Specific Populations

##### *Geriatric Patients*

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

##### *Patients with Hepatic Impairment*

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

##### *Patients with Renal Impairment*

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

## **13 NONCLINICAL TOXICOLOGY**

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

#### Carcinogenesis

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

## Mutagenesis

The mutagenic potential of bupivacaine hydrochloride has not been determined.

## Impairment of Fertility

The effect of bupivacaine on fertility has not been determined.

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

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

*Bupivacaine Hydrochloride Injection, USP*— Solutions of bupivacaine hydrochloride 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.

<b>Unit of Sale</b>	<b>Concentration</b>
<b>NDC 0409-1159-01</b> Tray of 25 single-dose teartop vials	0.25% <b>25 mg/10 mL</b> (2.5 mg/mL)
<b>NDC 0409-1159-02</b> Tray of 25 single-dose teartop vials	0.25% <b>75 mg/30 mL</b> (2.5 mg/mL)
<b>NDC 0409-1160-01</b> Tray of 25 multiple-dose flip-top vials	0.25% <b>125 mg/50 mL</b> (2.5 mg/mL)
<b>NDC 0409-1163-01</b> Tray of 25 multiple-dose flip-top vials	0.5% <b>250 mg/50 mL</b> (5 mg/mL)
<b>NDC 0409-1162-01</b> Tray of 25 single-dose teartop vials	0.5% <b>50 mg/10 mL</b> (5 mg/mL)
<b>NDC 0409-1162-02</b> Tray of 25 single-dose teartop vials	0.5% <b>150 mg/30 mL</b> (5 mg/mL)
<b>NDC 0409-1165-01</b> Tray of 25 single-dose teartop vials	0.75% <b>75 mg/10 mL</b> (7.5 mg/mL)
<b>NDC 0409-1165-02</b> Tray of 25 single-dose teartop vials	0.75% <b>225 mg/30 mL</b> (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](http://www.pfizer.com).

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LAB-1176-5.0

These highlights do not include all the information needed to use OMNIPAQUE safely and effectively. See full prescribing information for OMNIPAQUE.

OMNIPAQUE (iohexol) injection, for  
OMNIPAQUE (iohexol) oral solution  
Initial U.S. Approval: 1985

*See full prescribing information for complete boxed warning.*

Inadvertent intrathecal administration may cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema (4, 5).

**Warnings and Precautions.** Thyroid Dysfunction in Pediatric Patients 0 to 3 Years of Age (5.9)

4/2023

OMNIPAQUE (iohexol) injection is a radiographic contrast agent indicated for intrathecal, intravascular, oral, rectal, intraarticular and body cavity use. OMNIPAQUE oral solution is indicated for oral use only in conjunction with OMNIPAQUE injection administered intravenously for computed tomography (CT) of the abdomen (1).

**DOSAGE AND ADMINISTRATION**

The concentration and volume required will depend on the indication, size and condition of the patient, and the equipment and imaging technique used. For CT of the head and body, OMNIPAQUE may be used with an automated contrast injection system or contrast media management system cleared for use with OMNIPAQUE. See full prescribing information for complete dosing information (2).

### OMNIPAQUE Injection (3)

- 140 mg of iodine per mL (302 mg of iohexol/mL) in +PisaPak™ polymer bottles
- 180 mg of iodine per mL (388 mg of iohexol/mL) in glass vials
- 240 mg of iodine per mL (518 mg of iohexol/mL), 300 mg of iodine per mL (647 mg of iohexol/mL) and 350 mg of iodine per mL (755 mg of iohexol/mL) in glass vials and bottles and +PisaPak™ polymer bottles

**WARNING: RISKS WITH INADVERTENT INTRATHECAL ADMINISTRATION**

**WARNING: RISKS WITH INADVERTENT INTR.**  
**OMNIPAQUE injection, 140 and 350 mg iodine/mL**

#### 1 INDICATIONS AND USAGE

- INDICATIONS AND USAGE**
- 1.1 Intrathecal Administration
  - 1.2 Intravascular Administration
  - 1.3 Oral or Rectal Administration
  - 1.4 Oral Administration in Conjunction with Intravenous Administration
  - 1.5 Intraarticular Administration
  - 1.6 Body Cavity Administration

## 2 DOSAGE AND ADMINISTRATION

- ## 2 DOSAGE AND ADMINISTRATION
- 2.1 Important Dosage and Administration Instructions
  - 2.2 Intrathecal Dosage and Administration
  - 2.3 Intravascular Dosage and Administration
  - 2.4 Oral or Rectal Dosage and Administration
  - 2.5 Oral Dosage and Administration in Conjunction with Intravenous Administration
  - 2.6 Intraarticular Dosage and Administration
  - 2.7 Body Cavity Dosage and Administration
  - 2.8 Instructions for Use with an Automated Contrast Injection System or Contrast Management System for CT of the Head and Neck

### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 Risks Associated with Inadvertent Intrathecal Administration  
5.2 Risks Associated with Inadvertent Parenteral Administration  
5.3 Hypersensitivity Reactions  
5.4 Contrast-Induced Acute Kidney Injury  
5.5 Cardiovascular Adverse Reactions  
5.6 Thromboembolic Events  
5.7 Extravasation and Injection Site Reactions  
5.8 Thyroid Storm in Patients with Hyperthyroidism  
5.9 Thyroid Dysfunction in Pediatric Patients 0 to 3 Years of Age

## OMNIPAQUE Oral Solution (3)

- 9 mg of iodine per mL (19 mg of iohexol/mL) and 12 mg of iodine per mL (26 mg of iohexol/mL) in +PlusPak™ polymer bottles

#### CONTRAINDICATIONS

- CONTRAINDICATIONS**
- OMNIPAQUE injection 140 and 350 are contraindicated for intrathecal use (4)
  - OMNIPAQUE oral solution 9 and 12 are contraindicated for parenteral use (4)
  - OMNIPAQUE body cavity 240 and 300 for hysterosalpingography is contraindicated during pregnancy (or suspected pregnancy), menstruation (or when menstruation is imminent), within 6 months after termination of pregnancy, within 30 days after conization or curettage, when signs of infection are present in any portion of the genital tract, including the external genitalia, and when reproductive tract neoplasia is known or suspected. (4)

#### ..... WARNINGS AND PRECAUTIONS

- WARNINGS AND PRECAUTIONS**
- **Hypersensitivity Reactions:** Life-threatening or fatal reactions can occur. Always have emergency equipment and trained personnel available. (5.3)
  - **Contrast-Induced Acute Kidney Injury:** Acute injury including renal failure can occur. Minimize dose and maintain adequate hydration to minimize risk. (5.4)
  - **Cardiovascular Adverse Reactions:** Hemodynamic disturbances including shock and cardiac arrest may occur during or after administration. (5.5)
  - **Thyroid Dysfunction in Pediatric Patients 0 to 3 Years of Age:** Individualize thyroid function monitoring based on risk factors such as prematurity. (5.9)

#### ADVERSE REACTIONS

- Most common adverse reactions (incidence  $\geq 2.0\%$  in adult patients after OMNIPAC<sup>®</sup> administration. (6.1)**
- Intrathecal: Headaches, Pain including backache, neckache, stiffness and neuralgia, nausea, vomiting and dizziness
  - Intravascular: Pain, vision abnormalities (including blurred vision and photomas), headache, taste perversion, arrhythmias including premature ventricular contractions (PVCs) and premature atrial contractions (PACs), angina/chest pain, nausea
  - Oral: Diarrhea, nausea, vomiting, abdominal pain, flatulence, headache
  - Body Cavity: Pain, swelling and heat sensation

**Post-marketing adverse reactions (6.2):** Hypersensitivity and manifestations like rash, pruritus, urticaria, and dyspnea, in addition chest pain, and swelling.

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 1-800-654-0118 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**USE IN SPECIFIC POPULATIONS**

- **Lactation:** A lactating woman may pump and discard breast milk for 10 hours after OMNIPAQUE administration. (8.2)

**See 17 for PATIENT COUNSELING INFORMATION**

Revised: 4/2023

OMNIPAOUE 180

- Myelography (lumbar, thoracic, cervical, total columnar)
- CT (myelography, cisternography)

## **1.2 Intravascular Administration**

### Adults

#### OMNIPAQUE 140

- Intra-arterial digital subtraction angiography of the head, neck, abdominal, renal and peripheral vessels

#### OMNIPAQUE 240

- CT head imaging
- Peripheral venography (phlebography)

#### OMNIPAQUE 300

- Aortography including studies of the aortic arch, abdominal aorta and its branches
- CT head and body imaging
- Cerebral arteriography
- Peripheral venography (phlebography)
- Peripheral arteriography
- Excretory urography

#### OMNIPAQUE 350

- Angiocardiography (ventriculography, selective coronary arteriography)
- Aortography including studies of the aortic root, aortic arch, ascending aorta, abdominal aorta and its branches
- CT head and body imaging
- Intravenous digital subtraction angiography of the head, neck, abdominal, renal and peripheral vessels
- Peripheral arteriography
- Excretory urography

### Pediatrics

#### OMNIPAQUE 240

- CT head and body imaging

#### OMNIPAQUE 300

- Angiocardiography (ventriculography)
- Excretory urography
- CT head and body imaging

#### OMNIPAQUE 350

- Angiocardiography (ventriculography, pulmonary arteriography, venography, and studies of the collateral arteries)
- Aortography including the aortic root, aortic arch, ascending and descending aorta

## **1.3 Oral or Rectal Administration**

### Adults

#### OMNIPAQUE 350

- Oral radiographic examination of the gastrointestinal tract

#### Pediatrics

OMNIPAQUE 180, 240 and 300

- Oral and rectal radiographic examination of the gastrointestinal tract

### **1.4 Oral Administration in Conjunction with Intravenous Administration**

#### *Diluted OMNIPAQUE Injection*

##### Adults

OMNIPAQUE 240, 300 and 350 diluted and administered orally in conjunction with OMNIPAQUE 300 administered intravenously

- CT of the abdomen

##### Pediatrics

OMNIPAQUE 240, 300 and 350 diluted and administered orally in conjunction with OMNIPAQUE 240 or OMNIPAQUE 300 administered intravenously

- CT of the abdomen

#### *OMNIPAQUE Oral Solution*

##### Adults

OMNIPAQUE oral solution 9 and 12 administered orally in conjunction with OMNIPAQUE 300 administered intravenously

- CT of the abdomen

##### Pediatrics

OMNIPAQUE oral solution 9 and 12 administered orally in conjunction with OMNIPAQUE 240 or OMNIPAQUE 300 administered intravenously

- CT of the abdomen

### **1.5 Intraarticular Administration**

##### Adults

OMNIPAQUE 240, 300, and 350

- Arthrography

### **1.6 Body Cavity Administration**

##### Adults

OMNIPAQUE 240

- Endoscopic retrograde pancreatography (ERP) and cholangiopancreatography (ERCP)
- Herniography
- Hysterosalpingography

OMNIPAQUE 300

- Hysterosalpingography

## Pediatrics

OMNIPAQUE 240, 300 and 350 diluted

- Voiding cystourethrography (VCU)

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Important Dosage and Administration Instructions**

- OMNIPAQUE 140, 180, 240, 300 and 350 are indicated for intravascular, oral, rectal, intraarticular, and body cavity administration. OMNIPAQUE 180, 240, and 300 are indicated for intrathecal administration [see *Boxed Warning, Contraindications (4), and Warnings and Precautions (5.1)*].
- Use sterile technique for all handling and administration of OMNIPAQUE for intravascular, intrathecal, intraarticular, and body cavity administration.
- OMNIPAQUE oral solution 9 and 12 are indicated for oral use only [see *Contraindications (4) and Warnings and Precautions (5.2)*].
- Do not use if tamper-evident ring is broken or missing.
- OMNIPAQUE injection may be administered at either body (37°C, 98.6°F) or room temperature (20° to 25°C, 68° to 77°F).
- Inspect OMNIPAQUE injection for particulate matter or discoloration before administration, whenever solution and container permit. Do not administer if OMNIPAQUE injection contains particulate matter or is discolored.
- Do not mix OMNIPAQUE injection with, or inject in intravenous lines containing, other drugs or total nutritional admixtures.
- Use the lowest dose necessary to obtain adequate visualization.
- Individualize the volume, strength, and rate of administration of OMNIPAQUE injection. Consider factors such as age, body weight, vessel size, blood flow rate within the vessel, anticipated pathology, degree and extent of opacification required, structures or area to be examined, disease processes affecting the patient, and equipment and technique to be employed.
- Avoid extravasation when administering OMNIPAQUE injection intravascularly, especially in patients with severe arterial or venous disease [see *Warnings and Precautions (5.6)*].
- Hydrate patients before and after intravascular administration of OMNIPAQUE injection [see *Warnings and Precautions (5.4)*].
- Each bottle of OMNIPAQUE injection and oral solution is intended for one procedure only. Discard any unused portion.

### **2.2 Intrathecal Dosage and Administration**

- Rate of injection: Injection should be made slowly over 1 to 2 minutes
- Repeat procedures: If sequential or repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body; at least 48 hours should be allowed before repeat examination; however, whenever possible, 5 days to 7 days is recommended.
- If computerized tomographic (CT) myelography follows myelography, delay imaging several hours to allow the degree of contrast to decrease.

**TABLE 1 - INTRATHECAL ADULTS**

<b>The usual recommended total doses for use in lumbar, thoracic,</b>
---



**cervical, and total columnar myelography in adults are 1,200 mg iodine to 3,100 mg iodine (see below).**

<b>STUDY TYPE</b>	<b>INJECTION TYPE</b>	<b>CONCENTRATION (mg iodine/mL)</b>	<b>VOLUME (mL)</b>
LUMBAR MYELOGRAPHY	LUMBAR	OMNIPAQUE 180 OMNIPAQUE 240	10 to 17 7 to 12.5
THORACIC MYELOGRAPHY	LUMBAR CERVICAL	OMNIPAQUE 240 OMNIPAQUE 300	6 to 12.5 6 to 10
CERVICAL MYELOGRAPHY	LUMBAR	OMNIPAQUE 240 OMNIPAQUE 300	6 to 12.5 6 to 10
CERVICAL MYELOGRAPHY	C1-2	OMNIPAQUE 180 OMNIPAQUE 240 OMNIPAQUE 300	7 to 10 6 to 12.5 4 to 10
TOTAL COLUMNAR MYELOGRAPHY	LUMBAR	OMNIPAQUE 240 OMNIPAQUE 300	6 to 12.5 6 to 10

*\* A total dose of 3,100 mg iodine or a concentration of 300 mg iodine/mL should not be exceeded in adults.*

**TABLE 2 - INTRATHECAL PEDIATRICS**

**The usual recommended total doses for lumbar, thoracic, cervical, and/or total columnar myelography by lumbar puncture in children are 360 mg iodine to 2700 mg iodine (see below). Actual volumes administered depend largely on patient age and the following guidelines are recommended.**

<b>AGE</b>	<b>STUDY TYPE</b>	<b>INJECTION TYPE</b>	<b>CONCENTRATION (mg iodine/mL)</b>	<b>VOLUME (mL)</b>
0 up to 3 mos.	LUMBAR, THORACIC, CERVICAL AND/OR TOTAL COLUMNAR MYELOGRAPHY	LUMBAR PUNCTURE	OMNIPAQUE 180	2 to 4
3 up to 36 mos.			OMNIPAQUE 180	4 to 8
3 up to 7 yrs.			OMNIPAQUE 180	5 to 10
7 up to 13 yrs.			OMNIPAQUE 180	5 to 12
13 to 18 yrs.			OMNIPAQUE 180	6 to 15

*\*A total dose of 2,700 mg iodine or a concentration of 180 mg iodine/mL should not be exceeded in a single myelographic examination in pediatrics.*

## **2.3 Intravascular Dosage and Administration**

### Intra-arterial Procedures

**TABLE 3 ANGIOCARDIOGRAPHIC PROCEDURES**

<b>PATIENT POPULATION</b>	<b>CONCENTRATION (mg iodine/mL)</b>	<b>VOLUME (mL)</b>
		<u>VENTRICULOGRAPHY</u> • The recommended single dose is 40 mL

Adults	OMNIPAQUE 350	<p>(Range of 30 mL to 60 mL)</p> <ul style="list-style-type: none"> <li>May be combined with selective coronary arteriography</li> </ul> <p><u>SELECTIVE CORONARY ARTERIOGRAPHY</u></p> <ul style="list-style-type: none"> <li>The recommended single dose is 5 mL (Range of 3 mL to 14 mL)</li> </ul> <p>Doses may be repeated as necessary. Maximum volume with multiple injections should not exceed 250 mL.</p>
Pediatrics	OMNIPAQUE 300	<p><u>VENTRICULOGRAPHY</u></p> <p>The recommended single dose is 1.75 mL/kg (Range of 1.5 mL/kg to 2 mL/kg)</p> <ul style="list-style-type: none"> <li>May be repeated as necessary</li> </ul> <p>Maximum dose with multiple injections should not exceed 6 mL/kg up to a total volume of 291 mL.</p>
	OMNIPAQUE 350	<p><u>VENTRICULOGRAPHY</u></p> <p>Recommended single dose is 1.25 mL/kg (Range of 1 mL/kg to 1.5 mL/kg).</p> <ul style="list-style-type: none"> <li>May be repeated as necessary</li> </ul> <p>Maximum dose with multiple injections should not exceed 5 mL/kg up to a total volume of 250 mL.</p> <p><u>PULMONARY ANGIOGRAPHY (PULMONARY ARTERIOGRAPHY AND/OR PULMONARY VENOGRAPHY)</u></p> <p>The recommended single dose is 1 mL/kg.</p>

**TABLE 4 AORTOGRAPHY**

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	VOLUME (mL)
Adults	OMNIPAQUE 300 and 350	<p><u>AORTOGRAPHY AND SELECTIVE VISCERAL ARTERIOGRAPHY</u></p> <p>The recommended single dose is:</p> <ul style="list-style-type: none"> <li>50 mL to 80 mL for the aorta (aortic arch, ascending aorta)</li> <li>30 mL to 60 mL for abdominal aorta and its branches (celiac, mesenteric, hepatic and splenic arteries)</li> <li>5 mL to 15 mL for renal arteries</li> </ul> <p>Injections may be repeated if indicated, but the total volume should not exceed:</p> <ul style="list-style-type: none"> <li>290 mL of OMNIPAQUE 300</li> <li>250 mL of OMNIPAQUE 350</li> </ul>

	OMNIPAQUE 350	<u>AORTIC ROOT AND ARCH STUDY WHEN USED ALONE</u> The recommended single dose is 50 mL (Range of 20 mL to 75 mL)
Pediatrics	OMNIPAQUE 350	<u>AORTOGRAPHY (AORTIC ROOT, AORTIC ARCH, AND DESCENDING AORTA)</u> The recommended single dose is 1 mL/kg. <ul style="list-style-type: none"> <li>• May be repeated as necessary</li> </ul> Maximum dose should not exceed 5 mL/kg up to a total volume of 250 mL.

**TABLE 5 CEREBRAL ARTERIOGRAPHY**

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	VOLUME (mL)
Adults	OMNIPAQUE 300	Single dose for cerebral arteriography is as follows: <ul style="list-style-type: none"> <li>• Common carotid artery (6 mL to 12 mL)</li> <li>• Internal carotid artery (8 mL to 10 mL)</li> <li>• External carotid artery (6 mL to 9 mL)</li> <li>• Vertebral artery (6 mL to 10 mL)</li> </ul>

**TABLE 6 INTRA-ARTERIAL DIGITAL SUBTRACTION ANGIOGRAPHY HEAD, NECK, ABDOMINAL, RENAL AND PERIPHERAL VESSELS**

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	VOLUME (mL)		
Adults	OMNIPAQUE 140	ARTERIES	VOLUME/INJECTION (mL)	RATE OF INJECTION (mL/sec)
		Aorta	20 to 45	8 to 20
		Carotid	5 to 10	3 to 6
		Femoral	9 to 20	3 to 6
		Vertebral	4 to 10	2 to 8
		Renal	6 to 12	3 to 6
		Other branches of aorta (includes subclavian, axillary, innominate and iliac)	8 to 25	3 to 10

*Mechanical or hand injection can be used to administer one or more bolus intra-arterial injections of OMNIPAQUE 140.*

**TABLE 7 PERIPHERAL ARTERIOGRAPHY**

<b>PATIENT POPULATION</b>	<b>CONCENTRATION (mg iodine/mL)</b>	<b>VOLUME (mL)</b>
Adults	OMNIPAQUE 300 and 350	<p>The recommended dose for use in peripheral angiography is as follows:</p> <p>Aortofemoral runoffs:</p> <ul style="list-style-type: none"> <li>• 30 mL to 90 mL of OMNIPAQUE 300</li> <li>• 20 mL to 70 mL of OMNIPAQUE 350</li> </ul> <p>Selective arteriograms:</p> <ul style="list-style-type: none"> <li>• 10 mL to 60 mL of OMNIPAQUE 300</li> <li>• 10 mL to 30 mL of OMNIPAQUE 350</li> </ul>

### Intravenous Procedures

**TABLE 8 PERIPHERAL VENOGRAPHY (PHLEBOGRAPHY)**

<b>PATIENT POPULATION</b>	<b>CONCENTRATION (mg iodine/mL)</b>	<b>VOLUME (mL)</b>
Adults	OMNIPAQUE 240 and 300	<p>The recommended dose (per leg) is:</p> <ul style="list-style-type: none"> <li>• 20 mL to 150 mL of OMNIPAQUE 240</li> <li>• 40 mL to 100 mL of OMNIPAQUE 300</li> </ul>

**TABLE 9 EXCRETORY UROGRAPHY**

<b>PATIENT POPULATION</b>	<b>CONCENTRATION (mg iodine/mL)</b>	<b>VOLUME (mL)</b>
Adults	OMNIPAQUE 300 and 350	<p>The recommended dose is:</p> <ul style="list-style-type: none"> <li>• 0.6 mL/kg to 1.2 mL/kg body weight</li> </ul>
Pediatrics	OMNIPAQUE 300	<p>Dose ranging from 0.5 mL/kg to 3 mL/kg of body weight:</p> <ul style="list-style-type: none"> <li>• The usual dose for children is 1 mL/kg to 1.5 mL/kg.</li> <li>• The total administered dose should not exceed 3 mL/kg.</li> </ul>

**TABLE 10 DIGITAL SUBTRACTION ANGIOGRAPHY HEAD, NECK, ABDOMINAL, RENAL AND PERIPHERAL VESSELS**

<b>PATIENT POPULATION</b>	<b>CONCENTRATION (mg iodine/mL)</b>	<b>VOLUME (mL)</b>	<b>RATE OF INJECTION (mL/sec)</b>
Adults	OMNIPAQUE 350	<p>The usual dose for the intravenous digital technique is 30 mL to 50 mL.</p> <p>Frequently three or more</p>	<p>7.5 mL/second to 30 mL/second using a pressure</p>

		doses may be required, up to a total volume not to exceed 250 mL	injector
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**TABLE 11 CT SCANNING OF THE HEAD AND BODY**

<b>PATIENT POPULATION</b>	<b>CONCENTRATION (mg iodine/mL)</b>	<b>VOLUME * (mL)</b>
Adults	OMNIPAQUE 240, 300 and 350	<p><u>Head and body imaging by rapid injection</u></p> <p><b>CT Imaging - Head:</b></p> <ul style="list-style-type: none"> <li>• 70 mL to 150 mL of OMNIPAQUE 300</li> <li>• 80 mL of OMNIPAQUE 350</li> </ul> <p><b>CT Imaging - Body:</b></p> <ul style="list-style-type: none"> <li>• 50 mL to 200 mL of OMNIPAQUE 300</li> <li>• 60 mL to 100 mL of OMNIPAQUE 350</li> </ul> <p><u>Head imaging by infusion</u></p> <p><b>CT Imaging - Head:</b></p> <ul style="list-style-type: none"> <li>• 120 mL to 250 mL of OMNIPAQUE 240</li> </ul>
Pediatrics	OMNIPAQUE 240 and 300	<p><b>CT Imaging - Head and Body:</b></p> <ul style="list-style-type: none"> <li>• 1 mL/kg to 2 mL/kg (with maximum = 3 mL/kg)</li> <li>• Maximum single dose = 116 mL</li> </ul>

\* OMNIPAQUE may be used with an automated contrast injection system or contrast management system cleared for use with OMNIPAQUE [see Dosage and Administration (2.8)]. See device labeling for device indications, additional information, and instructions for use.

## 2.4 Oral or Rectal Dosage and Administration

Oral and Rectal Administration – Undiluted OMNIPAQUE Injection for Radiographic Examination of the Gastrointestinal (GI) Tract

**TABLE 12 DOSING FOR RADIOGRAPHIC EXAMINATION OF THE GI TRACT**

<b>PATIENT POPULATION</b>	<b>CONCENTRATION (mg iodine/mL)</b>	<b>ORAL VOLUME (mL)</b>	<b>RECTAL VOLUME * (mL)</b>
Adults	OMNIPAQUE 350	The recommended dose is 50 mL to 100 mL	-
		The recommended	The recommended

Pediatrics	OMNIPAQUE 180, 240 and 300	The recommended dose is 5 mL to 100 mL	The recommended dose is 5 mL to 100 mL *
Less than 3 months old	OMNIPAQUE 180	5 mL to 30 mL	- *
Three months to 3 years	OMNIPAQUE 180, 240 and 300	Up to 60 mL	- *
Four years to 10 years	OMNIPAQUE 180, 240 and 300	Up to 80 mL	- *
Greater than 10 years		Up to 100 mL	- *

\* When given rectally, larger volumes may be used.

## 2.5 Oral Dosage and Administration in Conjunction with Intravenous Administration

See Table 16 for concurrent intravenous dosing.

Oral Administration of Diluted OMNIPAQUE Injection in Conjunction with Intravenous Administration of OMNIPAQUE Injection for CT of the Abdomen

**TABLE 13 DOSING OF DILUTED \*OMNIPAQUE INJECTION FOR ORAL ADMINISTRATION**

PATIENT POPULATION	ORAL CONCENTRATION (mg iodine/mL)	ORAL VOLUME (mL)	ADMINISTRATION INSTRUCTIONS
Adults	OMNIPAQUE 240, 300 and 350 DILUTED to 6 to 12 mg iodine/mL (See Table 14 below)	Recommended oral dose is: <ul style="list-style-type: none"> <li>500 mL to 1,000 mL</li> </ul>	Smaller administered volumes can be given if the iodine concentration in final diluted product is increased (See Table 14 below) The oral dosage may be given all at once or over a period of up to 45 minutes if there is difficulty in consuming the required volume.
Pediatrics	OMNIPAQUE 240, 300 and 350 DILUTED to 9 to 21 mg iodine/mL	Recommended oral dose is: <ul style="list-style-type: none"> <li>180 mL to 750 mL</li> </ul> Do not exceed an oral dose of 5 grams iodine for	Smaller administered volumes can be given if the iodine concentration in final diluted product is increased (See Table 14 below) The oral dosage

	mg iodine/mL (See Table 14 below)	patients less than 3 years old. Do not exceed an oral dose of 10 grams iodine for patients 3 to 18 years old.	The oral dosage may be given all at once or over a period of up to 45 minutes if there is difficulty in consuming the required volume.
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\* Dilutions of OMNIPAQUE should be prepared just prior to use and any unused portion discarded after the procedure.

**TABLE 14 PROCEDURE FOR PREPARATION OF DILUTED OMNIPAQUE INJECTION FOR ORAL ADMINISTRATION**

**OMNIPAQUE to be mixed with liquid such as water, carbonated beverage, milk, infant formula, or juice to achieve one liter of oral contrast agent.**

Final Iodine Concentration of Diluted Contrast Agent (mg iodine/mL)	OMNIPAQUE 240		OMNIPAQUE 300		OMNIPAQUE 350	
	Volume of Contrast Agent (mL)	Volume of Liquid (mL)	Volume of Contrast Agent (mL)	Volume of Liquid (mL)	Volume of Contrast Agent (mL)	Volume of Liquid (mL)
6	25	975	20	980	17	983
9	38	962	30	970	26	974
12	50	950	40	960	35	965
15	63	937	50	950	43	957
18	75	925	60	940	52	948
21	88	912	70	930	60	940

Oral Administration of OMNIPAQUE Oral Solution in Conjunction with Intravenous Administration of OMNIPAQUE Injection for CT of the Abdomen

**TABLE 15 DOSING AND ADMINISTRATION OF OMNIPAQUE ORAL SOLUTION**

PATIENT POPULATION	ORAL CONCENTRATION (mg iodine/mL)	ORAL VOLUME (mL)	ADMINISTRATION INSTRUCTIONS
Adults	OMNIPAQUE oral solution 9 and 12	The recommended oral dose is: <ul style="list-style-type: none"> <li>500 mL to 1,000 mL</li> </ul>	The oral dosage may be given all at once or over a period of up to 45 minutes if there is difficulty in consuming the required volume.
		The recommended oral dose is:	

Pediatrics	OMNIPAQUE oral solution 9 and 12	<ul style="list-style-type: none"> <li>• 180 mL to 750 mL</li> </ul> Do not exceed an oral dose of 5 grams iodine for patients less than 3 years old. Do not exceed an oral dose of 10 grams iodine for patients 3 to 18 years old.	The oral dosage may be given all at once or over a period of up to 45 minutes if there is difficulty in consuming the required volume.
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**TABLE 16 INTRAVENOUS ADMINISTRATION OF OMNIPAQUE INJECTION FOR CT OF THE ABDOMEN IN CONJUNCTION WITH ORALLY ADMINISTERED DILUTED OMNIPAQUE INJECTION OR OMNIPAQUE ORAL SOLUTION**

PATIENT POPULATION	INTRAVENOUS CONCENTRATION (mg iodine/mL)	INTRAVENOUS VOLUME * (mL)	ADMINISTRATION INSTRUCTIONS
Adults	OMNIPAQUE 300	The recommended dose is: <ul style="list-style-type: none"> <li>• 100 mL to 150 mL</li> </ul>	Administer up to 40 minutes AFTER consumption of the oral dose
Pediatrics	OMNIPAQUE 240 and 300	The recommended dose is: <ul style="list-style-type: none"> <li>• 2 mL/kg with a range of 1 mL/kg to 2 mL/kg (maximum 3 mL/kg)</li> </ul>	Administer up to 60 minutes AFTER consumption of the oral dose

\* OMNIPAQUE may be used with an automated contrast injection system or contrast management system cleared for use with OMNIPAQUE [see Dosage and Administration (2.8)]. See device labeling for device indications, additional information, and instructions for use.

## 2.6 Intraarticular Dosage and Administration

**TABLE 17 ARTHROGRAPHY**

PATIENT POPULATION	LOCATION	CONCENTRATION (mg iodine/mL)	VOLUME (mL)	DOUBLE CONTRAST/SINGLE CONTRAST
Adults	Knee *	OMNIPAQUE 240	5 to 15	Lower volumes recommended for double-contrast examinations; higher volumes recommended for
		OMNIPAQUE 300	5 to 15	
		OMNIPAQUE 350	5 to 10	
Adults	Shoulder *	OMNIPAQUE 240	3	
		OMNIPAQUE 300	10	



Adults	Temporomandibular*	OMNIPAQUE 300	0.5 to 1	single-contrast examinations.
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\* Passive or active manipulation is used to disperse the medium throughout the joint space.

## 2.7 Body Cavity Dosage and Administration

### Body Cavity Administration - Undiluted OMNIPAQUE Injection

**TABLE 18 ENDOSCOPIC RETROGRADE PANCREATOGRAPHY (ERP)  
ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ECRP)**

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	VOLUME (mL)
Adults	OMNIPAQUE 240	10 mL to 50 mL but may vary depending on individual anatomy and/or disease state.

**TABLE 19 HYSTEROSALPINGOGRAPHY**

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	VOLUME (mL)
Adults	OMNIPAQUE 240 and 300	15 mL to 20 mL but may vary depending on individual anatomy and/or disease state.

**TABLE 20 HERNIOGRAPHY**

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	VOLUME (mL)
Adults	OMNIPAQUE 240	50 mL but may vary depending on individual anatomy and/or disease state.

### Body Cavity Administration - Diluted OMNIPAQUE Injection

**TABLE 21 VOIDING CYSTOURETHROGRAPHY (VCU) (CAN BE PERFORMED IN CONJUNCTION WITH EXCRETORY UROGRAPHY)**

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	VOLUME (mL)
Pediatrics	The concentration may vary depending upon the patient's size and age and with the technique and equipment used. OMNIPAQUE injection may be diluted with Sterile	OMNIPAQUE injection may be diluted, utilizing aseptic technique, with Sterile Water for Injection to a concentration of 50 mg iodine/mL to 100 mg iodine/mL for voiding cystourethrography. Range: <ul style="list-style-type: none"> <li>50 mL to 300 mL of DILUTED OMNIPAQUE at a concentration of 100 mg iodine/mL</li> </ul>

mixed with Sterile Water for Injection. (See Table 22 below).

- 50 mL to 600 mL of DILUTED OMNIPAQUE at a concentration of 50 mg iodine/mL.

**TABLE 22 PROCEDURE FOR PREPARATION OF DILUTED \*OMNIPAQUE INJECTION FOR VCU**

Final Iodine Concentration of Diluted Contrast Agent (mg iodine/mL)	Volume of OMNIPAQUE 240 (mL)	Volume of Sterile Water for Injection (mL)	Volume of OMNIPAQUE 300 (mL)	Volume of Sterile Water for Injection (mL)	Volume of OMNIPAQUE 350 (mL)	Volume of Sterile Water for Injection (mL)
100	100	140	100	200	100	250
90		167		233		289
80		200		275		338
70		243		330		400
60		300		400		483
50		380		500		600

\* Dilutions of OMNIPAQUE should be prepared just prior to use and any unused portion discarded after the procedure.

## 2.8 Instructions for Use with an Automated Contrast Injection System or Contrast Management System for CT of the Head and Body

- OMNIPAQUE may be used with an automated contrast injection system cleared for use with contrast media.
  - See above Important Dosage and Administration Instructions for OMNIPAQUE (2.1).
  - See device labeling for information on device indications, instructions for use, and techniques to help assure safe use.
- OMNIPAQUE 300 mg iodine/mL and 350 mg iodine/mL in 150 mL bottles may be used with a contrast media management system cleared for use with OMNIPAQUE 300 mg iodine/mL and 350 mg iodine/mL in 150 mL bottles.
  - See device labeling for information on device indications, instructions for use, and techniques to help assure safe use.
  - Use sterile technique for penetrating the container closure of OMNIPAQUE 300 and 350 and transferring OMNIPAQUE solution. The container closure may be penetrated only one time with a suitable sterile component of the contrast media management system cleared for use with OMNIPAQUE 300 and 350 in 150 mL bottles.
  - Once the OMNIPAQUE 300 and 350 Injection is punctured, do not remove the bottle from the work area during the entire period of use.
  - Maximum use time is 4 hours after initial puncture.
  - Each bottle is for one procedure only. Discard unused portion.

## 3 DOSAGE FORMS AND STRENGTHS

## **OMNIPAQUE (iohexol) Injection and Oral Solution**

Sterile, pyrogen-free, gluten-free, colorless to pale yellow solution containing the nonionic, water-soluble x-ray contrast medium iohexol, and available in the following strengths and formats:

### **OMNIPAQUE (iohexol) Injection**

- 140 mg of organically bound iodine per mL (302 mg iohexol/mL)
  - Available in + *PLUSPAK*™ (polymer bottle)
- 180 mg of organically bound iodine per mL (388 mg iohexol/mL)
  - Available in glass vials
- 240 mg of organically bound iodine per mL (518 mg iohexol/mL)
- 300 mg of organically bound iodine per mL (647 mg iohexol/mL)
- 350 mg of organically bound iodine per mL (755 mg iohexol/mL)
  - Available in glass vials and bottles and + *PLUSPAK*™ polymer bottles.

### **OMNIPAQUE Oral Solution**

- 9 mg of organically bound iodine per mL (19 mg iohexol/mL)
- 12 mg of organically bound iodine per mL (26 mg iohexol/mL)
  - Available in + *PLUSPAK*™ polymer bottles.

## **4 CONTRAINDICATIONS**

- OMNIPAQUE 140 and OMNIPAQUE 350 are contraindicated for intrathecal use [*see Warnings and Precautions (5.1)*]
- OMNIPAQUE oral solution 9 and 12 are contraindicated for parenteral administration [*see Warnings and Precautions (5.2)*]
- OMNIPAQUE body cavity 240 and 300 for hysterosalpingography is contraindicated during pregnancy or suspected pregnancy, menstruation or when menstruation is imminent, within 6 months after termination of pregnancy, within 30 days after conization or curettage, when signs of infection are present in any portion of the genital tract including the external genitalia, and when reproductive tract neoplasia is known or suspected because of the risk of peritoneal spread of neoplasm.

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Risks Associated with Inadvertent Intrathecal Administration**

OMNIPAQUE injection 140 and 350 are contraindicated for intrathecal use [*see Contraindications (4) and Dosage and Administration (2.1)*]. Inadvertent intrathecal administration can cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema.

### **5.2 Risks Associated with Inadvertent Parenteral Administration**

OMNIPAQUE oral solution 9 and 12 are contraindicated for parenteral administration [*see Contraindications (4) and Dosage and Administration (2.1)*]. Adverse reactions such as hemolysis may occur if administered intravascularly. Do not administer OMNIPAQUE oral solution 9 and 12 parenterally.

### **5.3 Hypersensitivity Reactions**

OMNIPAQUE can cause life-threatening or fatal hypersensitivity reactions including anaphylaxis. Manifestations include respiratory arrest, laryngospasm, bronchospasm, angioedema, and shock. Most severe reactions develop shortly after the start of the injection (within 3 minutes), but reactions can occur up to hours later. There is an increased risk in patients with a history of a previous reaction to contrast agent, and known allergies (i.e., bronchial asthma, drug, or food allergies) or other hypersensitivities. Premedication with antihistamines or corticosteroids does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

Obtain a history of allergy, hypersensitivity, or hypersensitivity reactions to iodinated contrast agents and always have emergency resuscitation equipment and trained personnel available prior to OMNIPAQUE administration. Monitor all patients for hypersensitivity reactions.

#### **5.4 Contrast-Induced Acute Kidney Injury**

Acute kidney injury, including renal failure, may occur after parenteral administration of OMNIPAQUE. Risk factors include: pre-existing renal impairment, dehydration, diabetes mellitus, congestive heart failure, advanced vascular disease, elderly age, concomitant use of nephrotoxic or diuretic medications, multiple myeloma/paraproteinaceous diseases, repetitive and/or large doses of an iodinated contrast agent.

Use the lowest necessary dose of OMNIPAQUE in patients with renal impairment. Adequately hydrate patients prior to and following parenteral administration of OMNIPAQUE. Do not use laxatives, diuretics, or preparatory dehydration prior to OMNIPAQUE administration.

#### **5.5 Cardiovascular Adverse Reactions**

Life-threatening or fatal cardiovascular reactions including hypotension, shock, cardiac arrest have occurred with the parenteral administration of OMNIPAQUE. Most deaths occur during injection or five to ten minutes later, with cardiovascular disease as the main aggravating factor. Cardiac decompensation, serious arrhythmias, and myocardial ischemia or infarction can occur during coronary arteriography and ventriculography.

Based upon clinical literature reported deaths from the administration of iodinated contrast agents range from 6.6 per million (0.00066%) to 1 in 10,000 (0.01%). Use the lowest necessary dose of OMNIPAQUE in patients with congestive heart failure and always have emergency resuscitation equipment and trained personnel available. Monitor all patients for severe cardiovascular reactions.

#### **5.6 Thromboembolic Events**

##### Angiocardiology

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke can occur during angiocardiology procedures with both ionic and nonionic contrast media. During these procedures, increased thrombosis and activation of the complement system occurs. Risk factors for thromboembolic events include: length of procedure, catheter and syringe material, underlying disease state, and concomitant medications.

To minimize thromboembolic events, use meticulous angiographic techniques, and minimize the length of the procedure. Avoid blood remaining in contact with syringes

containing iodinated contrast agents, which increases the risk of clotting. Avoid angiocardiology in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

### **5.7 Extravasation and Injection Site Reactions**

Extravasation of OMNIPAQUE during intravascular injection may cause tissue necrosis and/or compartment syndrome, particularly in patients with severe arterial or venous disease. Ensure intravascular placement of catheters prior to injection. Monitor patients for extravasation and advise patients to seek medical care for progression of symptoms.

### **5.8 Thyroid Storm in Patients with Hyperthyroidism**

Thyroid storm has occurred after the intravascular use of iodinated contrast agents in patients with hyperthyroidism, or with an autonomously functioning thyroid nodule. Evaluate the risk in such patients before use of OMNIPAQUE.

### **5.9 Thyroid Dysfunction in Pediatric Patients 0 to 3 Years of Age**

Thyroid dysfunction characterized by hypothyroidism or transient thyroid suppression has been reported after both single exposure and multiple exposures to iodinated contrast media (ICM) in pediatric patients 0 to 3 years of age.

Younger age, very low birth weight, prematurity, underlying medical conditions affecting thyroid function, admission to neonatal or pediatric intensive care units, and congenital cardiac conditions are associated with an increased risk of hypothyroidism after ICM exposure. Pediatric patients with congenital cardiac conditions may be at the greatest risk given that they often require high doses of contrast during invasive cardiac procedures.

An underactive thyroid during early life may be harmful for cognitive and neurological development and may require thyroid hormone replacement therapy. After exposure to ICM, individualize thyroid function monitoring based on underlying risk factors, especially in term and preterm neonates.

### **5.10 Hypertensive Crisis in Patients with Pheochromocytoma**

Hypertensive crisis has occurred after the use of iodinated contrast agents in patient with pheochromocytoma. Monitor patients when administering OMNIPAQUE intravascularly if pheochromocytoma or catecholamine-secreting paragangliomas are suspected. Inject the minimum amount of contrast necessary, assess the blood pressure throughout the procedure, and have measures for treatment of a hypertensive crisis readily available.

### **5.11 Sickle Cell Crisis in Patients with Sickle Cell Disease**

Iodinated contrast agents when administered intravascularly may promote sickling in individuals who are homozygous for sickle cell disease. Hydrate patients prior to and following OMNIPAQUE administration and use OMNIPAQUE only if the necessary imaging information cannot be obtained with alternative imaging modalities.

### **5.12 Severe Cutaneous Adverse Reactions**

Severe cutaneous adverse reactions (SCAR) may develop from 1 hour to several weeks

after intravascular contrast agent administration. These reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS). Reaction severity may increase and time to onset may decrease with repeat administration of contrast agents; prophylactic medications may not prevent or mitigate severe cutaneous adverse reactions. Avoid administering OMNIPAQUE to patients with a history of a severe cutaneous adverse reaction to OMNIPAQUE.

## 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Risks Associated with Inadvertent Intrathecal Administration *[see Warnings and Precautions (5.1)]*
- Risks Associated with Inadvertent Parenteral Administration *[see Warnings and Precautions (5.2)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Contrast-Induced Kidney Injury *[see Warnings and Precautions (5.4)]*
- Cardiovascular Adverse Reactions *[see Warnings and Precautions (5.5)]*
- Thromboembolic Events *[see Warnings and Precautions (5.6)]*
- Thyroid Dysfunction in Pediatric Patients 0 to 3 Years of Age *[see Warnings and Precautions (5.9)]*
- Severe Cutaneous Adverse Reactions *[ see Warnings and Precautions (5.12)]*

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

#### Intrathecal Administration

##### *Adults*

**TABLE 23 ADVERSE REACTIONS - INTRATHECAL ADMINISTRATION**

<b>In controlled clinical studies involving 1531 patients using OMNIPAQUE the following adverse reactions were reported:</b>		
<b>System Organ Class</b>	<b>Adverse Reaction</b>	<b>Incidence</b>
Nervous System	Headaches	18%
Musculoskeletal and Connective Tissue	Pain including backache, neckache, stiffness and neuralgia	8%
Gastrointestinal System	Nausea	6%
	Vomiting	3%
Nervous System	Dizziness	2%
Other Reactions	Feeling of heaviness, hypotension, hypertonia, sensation of heat, sweating, vertigo, loss of appetite, drowsiness, hypertension, photophobia, tinnitus, neuralgia, paresthesia, difficulty in micturition,	<0.1%

and neurological changes

## Pediatric Patients

**TABLE 24 ADVERSE REACTIONS - INTRATHECAL ADMINISTRATION**

**In clinical studies involving 152 patients for pediatric myelography by lumbar puncture, adverse events following the use of OMNIPAQUE 180 were generally similar to those reported in adults.**

Procedure	System Organ Class	Adverse Reaction	Incidence
Myelography by Lumbar Puncture	Nervous System	Headache	9%
	Gastrointestinal System	Vomiting	6%
	Musculoskeletal and Connective Tissue	Backache	1.3%
	Other Reactions <i>All were transient and mild with no clinical sequelae.</i>	Fever	<0.7%
		Hives	
		Stomachache	
		Visual Hallucination	
		Neurological Changes	

## Intravascular Administration

Immediately following intravascular injection of contrast medium, a transient sensation of mild warmth is not unusual. Warmth is less frequent with OMNIPAQUE than with ionic contrast media.

## Adults

In controlled clinical studies involving 1485 patients, the following adverse reactions occurred (Table 25).

**TABLE 25 ADVERSE REACTIONS - INTRAVASCULAR ADMINISTRATION**

System Organ Class	Adverse Reaction	Incidence
Cardiovascular System	Arrhythmias including PVCs and PACs	2%
	Hypotension	0.7%
	Others including cardiac failure, asystole, bradycardia, tachycardia, and vasovagal reaction	≤ 0.3%
Nervous System	Vertigo (including dizziness and lightheadedness)	0.5%
	Pain	3%
	Vision Abnormalities (including blurred vision and photomas)	2%
	Taste Perversion	1%
Other Reactions	Anxiety, fever, motor and speech dysfunction, convulsion, paresthesia, somnolence, stiff neck, hemiparesis,	Individual incidence of

Other Reactions	syncope, shivering, transient ischemic attack, cerebral infarction, and nystagmus	Incidence of 0.3% or less
Respiratory System	Dyspnea, rhinitis, coughing, and laryngitis	Individual incidence of 0.2% or less
Gastrointestinal System	Nausea	2%
	Vomiting	0.7%
	Others including diarrhea, dyspepsia, cramp, and dry mouth	Individual incidence of less than 0.1%.
Skin and Subcutaneous Tissues	Urticaria	0.3%
	Purpura	0.1%
	Abscess	0.1%
	Pruritus	0.1%

### *Pediatric Patients*

In controlled clinical studies involving 391 patients for pediatric angiocardiology, urography, and CT head imaging, adverse reactions following the use of OMNIPAQUE 240, 300, and 350 were generally similar in quality and frequency to those reported in adults (Table 26).

**TABLE 26 ADVERSE REACTIONS - INTRAVASCULAR ADMINISTRATION**

<b>System Organ Class</b>	<b>Adverse Reaction</b>	<b>Incidence</b>
Cardiovascular System	Ventricular Tachycardia	0.5%
	2:1 Heart Block	0.5%
	Hypertension	0.3%
	Anemia	0.3%
General Disorders and Administration Site Conditions	Pain	0.8%
	Fever	0.5%
Nervous System	Convulsion	0.3%
	Taste Abnormality	0.5%
Respiratory System	Congestion	0.3%
	Apnea	0.3%
Gastrointestinal System	Nausea	1%
	Vomiting	2%
Endocrine System	Hypoglycemia	0.3%
Skin and Subcutaneous Tissue	Rash	0.3%

### Oral Administration for Examination of the Gastrointestinal Tract

#### *Adults*

Nausea, vomiting, and diarrhea have been most frequently reported following orally administered undiluted OMNIPAQUE for radiographic examination of the gastrointestinal



tract. In controlled clinical studies involving 54 adult patients for oral radiographic examination of the gastrointestinal tract using undiluted OMNIPAQUE 350 the following adverse reactions were reported (Table 27).

**TABLE 27 ADVERSE REACTIONS - ORAL ADMINISTRATION OF UNDILUTED OMNIPAQUE 350**

<b>System Organ Class</b>	<b>Adverse Reaction</b>	<b>Incidence</b>
Gastrointestinal System	Diarrhea	42%
	Nausea	15%
	Vomiting	11%
	Abdominal Pain	7%
	Flatulence	2%
Nervous System	Headache	2%

*Pediatrics Patients (Oral and Rectal Administration)*

In clinical studies involving 58 pediatric patients, the adverse reactions were found to mostly affect the gastrointestinal system with diarrhea (36%), vomiting (9%), nausea (5%) and abdominal pain (2%). However, fever (5%), hypotension (2%) and urticaria (2%) were also reported.

Oral Administration for CT of the Abdomen in Conjunction with Intravenous Administration

*Adults*

In a controlled clinical study involving 44 adult patients receiving oral administration of diluted OMNIPAQUE (4-9 mg iodine/mL) in conjunction with intravenously injected OMNIPAQUE 300 for CT examination of the abdomen, adverse reactions were limited to a single report of vomiting.

*Pediatric Patients*

In clinical studies involving 69 pediatric patients receiving oral administration of diluted OMNIPAQUE (9-29 mg iodine/mL) in conjunction with intravenously administered OMNIPAQUE 240 and OMNIPAQUE 300 for CT examination of the abdomen, adverse reactions were limited to a single report of vomiting (1.4%).

Body Cavity Use

*Adults*

Arthrography: In controlled clinical studies involving 285 adult patients for various body cavity examinations using OMNIPAQUE 240, 300 and 350, the most frequent adverse reactions were administration site reactions: pain 26% and swelling 22%, were exclusively reported for arthrography and were generally related to the procedure rather than the contrast medium. Patients also experienced heat (7%). All other adverse reaction occurred at a rate less than or equal to 1%.

*Pediatric Patients*

No adverse reactions associated with the use of OMNIPAQUE for VCU procedures were reported in 51 pediatric patients studied.

## 6.2 Post-marketing Experience

The following additional reactions listed by indication have been identified during post-approval use of OMNIPAQUE. Because these reactions are 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.

### General

*Immune System Disorders:* Hypersensitivity reactions, anaphylactic or anaphylactoid reactions, anaphylactic or anaphylactoid shock including life-threatening or fatal anaphylaxis

*General Disorders and Administration Site Conditions:* Pyrexia, chills, pain and discomfort, asthenia, administration site conditions including extravasation

### Intrathecal Administration

*Nervous System Disorders:* Meningism, aseptic meningitis, seizures or status epilepticus, disorientation, coma, depressed or loss of consciousness, transient contrast-induced toxic encephalopathy (including amnesia, hallucination, paralysis, paresis, speech disorder, aphasia, dysarthria), restlessness, tremors, hypoesthesia

*Musculoskeletal and Connective Tissue Disorders:* Pain, muscle spasms or spasticity

*Psychiatric Disorders:* Confusional state, agitation, anxiety

*Eye Disorders:* Transient visual impairment including cortical blindness

*Renal Reactions:* Acute kidney injury

### Intravascular Administration

*Cardiovascular Disorders:* Severe cardiac complications (including cardiac arrest, cardiopulmonary arrest), shock, peripheral vasodilatation, palpitations, vasospasm including spasm of coronary arteries, myocardial infarction, syncope, cyanosis, pallor, flushing, chest pain

*Hemodynamic Reactions:* Vasospasm and thrombophlebitis following intravenous injection

*Blood and Lymphatic System Disorders:* Neutropenia

*Nervous System Disorders:* Disorientation, coma, depressed or loss of consciousness, transient contrast-induced toxic encephalopathy (including amnesia, hallucination, paralysis, paresis, speech disorder, aphasia, dysarthria), restlessness, tremors, hypoesthesia

*Psychiatric Disorders:* Confusional state, agitation

*Eye Disorders:* Eye irritation or itchiness, periorbital edema, ocular or conjunctival hyperemia, lacrimation

*Renal Reactions:* Acute kidney injury, toxic nephropathy (CIN), transient proteinuria, oliguria or anuria, increased serum creatinine

*Gastrointestinal Disorders:* Abdominal pain, pancreatitis aggravated, salivary gland enlargement

*Endocrine Reactions:* Hyperthyroidism, hypothyroidism

*Respiratory; Thoracic, and Mediastinal Disorders:* Respiratory distress, respiratory failure, pulmonary edema, bronchospasm, laryngospasm, throat irritation, throat tightness, laryngeal edema, wheezing, chest discomfort, asthmatic attack

*Skin and Subcutaneous Tissue Disorders:* Contrast media reactions range from mild (e.g., pleomorphic rashes, drug eruption, erythema and skin discoloration, blisters, hyperhidrosis, angioedema, localized areas of edema) to severe: [e.g., Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), bullous or exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS)]

#### Oral Administration

*Gastrointestinal Disorders:* Dysphagia, abdominal pain

#### Body Cavity Administration

*Gastrointestinal Disorders:* Pancreatitis

*Musculoskeletal and Connective Tissue Disorders:* Arthritis (arthrography)

*Hysterosalpingography:* Injection of OMNIPAQUE for hysterosalpingography is associated with immediate, transient pain. Monitor injection pressure and volume instilled to minimize pain and to avoid disruptive distention of the uterus and fallopian tubes. Fluoroscopic monitoring is recommended.

*Nervous system:* Pain (49%), somnolence and fever each with an individual incidence of 3%.

*Gastrointestinal system:* Nausea (3%)

## **7 DRUG INTERACTIONS**

### **7.1 Drug-Drug Interactions**

#### Metformin

In patients with renal impairment, metformin can cause lactic acidosis. Iodinated contrast agents appear to increase the risk of metformin-induced lactic acidosis, possibly as a result of worsening renal function. Stop metformin at the time of, or prior to, OMNIPAQUE administration in patients with an eGFR between 30 and 60 mL/min/1.73 m<sup>2</sup>; in patients with a history of hepatic impairment, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and reinstitute metformin only after renal function is stable.

#### Radioactive Iodine

Administration of iodinated contrast agents may interfere with thyroid uptake of radioactive iodine (I-131 and I-123) and decrease therapeutic and diagnostic efficacy in patients with carcinoma of the thyroid. The decrease in efficacy lasts for 6 to 8 weeks.

#### Beta-adrenergic Blocking Agents

The use of beta-adrenergic blocking agents lowers the threshold for and increases the severity of contrast reactions and reduces the responsiveness of treatment of hypersensitivity reactions with epinephrine. Because of the risk of hypersensitivity

reactions, use caution when administering OMNIPAQUE to patients taking beta-blockers.

### Drugs that Lower Seizure Threshold

Drugs that lower seizure threshold, especially phenothiazine derivatives including those used for their antihistaminic or antinauseant properties, are not recommended for use with intrathecal administration of OMNIPAQUE.

### CNS Active Drugs

Drugs such as monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, CNS stimulants, psychoactive drugs described as analeptics, major tranquilizers, or antipsychotic drugs. Such medications should be discontinued at least 48 hours before myelography, should not be used for the control of nausea or vomiting during or after myelography, and should not be resumed for at least 24 hours post procedure. In non-elective procedures in patients on these drugs, consider prophylactic use of anticonvulsants.

## **7.2 Drug-Laboratory Test Interactions**

### Effect on Thyroid Tests

If iodine-containing isotopes are to be administered for the diagnosis of thyroid disease, the iodine-binding capacity of thyroid tissue may be reduced for up to 2 weeks after contrast medium administration. Thyroid function tests that do not depend on iodine estimation, e.g., T<sub>3</sub> resin uptake or direct thyroxine assays, are not affected.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

Hysterosalpingography is contraindicated in pregnant women due to the potential risk to the fetus from an intrauterine procedure [see *Contraindications (4)*]. There are no data with iohexol use in pregnant women to inform any drug-associated risks. Iohexol crosses the placenta and reaches fetal tissues in small amounts (see *Data*). In animal reproduction studies, no developmental toxicity occurred with intravenous iohexol administration to rats and rabbits at doses up to 0.4 (rat) and 0.5 (rabbit) times the maximum recommended human intravenous dose ( see *Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

#### Data

##### *Human Data*

Literature reports show that intravenously administered iohexol crosses the placenta and is visualized in the digestive tract of exposed infants after birth.

##### *Animal Data*

Iohexol was neither embryotoxic nor teratogenic in either rats or rabbits at the following

dose levels tested: 1.0, 2.0, 4.0 g iodine/kg in rats, administered intravenously to 3 groups of 25 dams once daily during days 6 through 15 of pregnancy; 0.3, 1.0, 2.5 g iodine/kg in rabbits, administered intravenously to 3 groups of 18 rabbits dosed once a day during days 6 through 18 of pregnancy.

## **8.2 Lactation**

### Risk Summary

Published literature reports that breast feeding after intravenous iohexol administration to the mother would result in the infant receiving an oral dose of approximately 0.7% of the maternal intravenous dose; however, lactation studies have not been conducted with oral, intrathecal, or intracavity administration of iohexol. There is no information on the effects of the drug on the breastfed infant or on milk production. Iodinated contrast agents are excreted unchanged in human milk in very low amounts with poor absorption from the gastrointestinal tract of a breastfed infant. Exposure to iohexol to a breastfed infant can be minimized by temporary discontinuation of breastfeeding (see Clinical Considerations). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OMNIPAQUE and any potential adverse effects on the breastfed infant from OMNIPAQUE or from the underlying maternal condition.

### Clinical Considerations

Interruption of breastfeeding after exposure to iodinated contrast agents is not necessary because the potential exposure of the breastfed infant to iodine is small. However, a lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk for 10 hours (approximately 5 elimination half-lives) after OMNIPAQUE administration to minimize drug exposure to a breastfed infant.

## **8.4 Pediatric Use**

### Intrathecal Use

The safety and effectiveness of OMNIPAQUE 180 have been established in pediatric patients 2 weeks to 17 years of age for myelography (lumbar, thoracic, cervical, total columnar) and for CT (myelography, cisternography). Use of OMNIPAQUE 180 is supported by controlled clinical studies in adults for myelography, in addition to clinical studies in pediatric patients undergoing myelography. The safety and effectiveness of OMNIPAQUE 180 have not been established for intrathecal use in patient pediatric patients less than 2 weeks of age. The safety and effectiveness of OMNIPAQUE 240 and 300 have not been established in pediatric patients for myelography (lumbar, thoracic, cervical, total columnar) and for CT (myelography, cisternography, or ventriculography).

### Intravascular Use

*Angiocardiology( Ventriculography, Pulmonary Arteriography, Venography, and Studies of the Collateral Arteries) and Aortography*

The safety and effectiveness of OMNIPAQUE 300 have been established in pediatric patients from birth to 17 years of age for angiocardiology (ventriculography) and of OMNIPAQUE 350 in pediatric patients from birth to 17 years of age for angiocardiology (ventriculography, pulmonary arteriography, venography, and studies of the collateral arteries) and aortography. Use of OMNIPAQUE 300 and 350 is supported by controlled clinical studies in adults for angiocardiology and aortography,

in addition to controlled clinical studies in pediatric patients undergoing angiocardiology, including aortography. The safety and effectiveness of OMNIPAQUE 300 have not been established in pediatric patients for aortography.

*Intra-arterial Digital Subtraction Angiography, Intravenous Digital Subtraction Angiography, Cerebral Arteriography, or Peripheral Arteriography and Venography*

The safety and effectiveness of OMNIPAQUE have not been established in pediatric patients for intra-arterial digital subtraction angiography, intravenous digital subtraction angiography, cerebral arteriography, or peripheral arteriography and venography.

*CT of the Head and Body*

The safety and effectiveness of OMNIPAQUE 240 and 300 have been established in pediatric patients from birth to 17 years of age for CT imaging of the head and body. Use of OMNIPAQUE 240 and 300 is supported by controlled clinical studies in adults for head and body CT, in addition to clinical studies in pediatric patients undergoing head CT and in 69 pediatric patients undergoing CT of the abdomen after oral administration of diluted OMNIPAQUE plus intravenous administration of OMNIPAQUE. The safety and effectiveness of OMNIPAQUE 350 have not been established in pediatric patients for CT imaging of the head and body.

*Urography*

The safety and effectiveness of OMNIPQUE 300 have been established in pediatric patients from birth to 17 years of age for urography. Use of OMNIPAQUE 300 is supported by controlled clinical studies in adults for urography, in addition to controlled clinical studies in pediatric patients undergoing urography and clinical safety data in pediatric patients down to birth.

Oral or Rectal Use

*Undiluted OMNIPAQUE Injection*

The safety and effectiveness of OMNIPAQUE 180, 240, and 300 administered orally and rectally have been established in pediatric patients, from birth to 17 years of age for examination of the GI tract. Use of OMNIPAQUE 180, 240, and 300 administered orally and rectally is supported by controlled studies in adults for examination of the GI tract, in addition to clinical studies in pediatric patients undergoing examination of the GI tract.

Oral Use in Conjunction with Intravenous Use

*Diluted OMNIPAQUE Injection*

The safety and effectiveness of OMNIPAQUE injection diluted to concentrations from 9 to 21 mg iodine/mL administered orally in conjunction with OMNIPAQUE injection administered intravenously for CT of the abdomen have been established in pediatric patients from birth to 17 years of age. Use is supported by clinical trials in adults, in addition to clinical studies in 69 pediatric patients undergoing CT of the abdomen after oral administration of diluted OMNIPAQUE plus intravenous administration of OMNIPAQUE.

*OMNIPAQUE Oral Solution*

The safety and effectiveness of OMNIPAQUE oral solution 9 and 12 administered orally in conjunction with OMNIPAQUE injection administered intravenously for CT of the abdomen in pediatric patients have been established in pediatric patients from birth to 17 years of age. Use is supported by the data establishing safety and effectiveness for

OMNIPAQUE injection diluted and administered orally in conjunction with OMNIPAQUE injection administered intravenously for CT of the abdomen in pediatric patients.

### Intraarticular Use

The safety and effectiveness of OMNIPAQUE have not been established in pediatric patients for arthrography.

### Body Cavity Use

OMNIPAQUE 240, 300, 350 diluted to concentrations from 50 mg iodine/mL to 100 mg iodine/mL is indicated for use in pediatric patients from birth to 17 years of age for voiding cystourethrography (VCU). The use for voiding cystourethrography is supported by clinical studies in 51 pediatric patients undergoing VCU. The safety and effectiveness of OMNIPAQUE have not been established in pediatric patients for ERCP, herniography, or hysterosalpingography.

In general, the frequency of adverse reactions in pediatric patients was similar to that seen in adults [*see Adverse Reactions (6.1)*]. Pediatric patients at higher risk of experiencing adverse events during contrast-medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

Thyroid function tests indicative of thyroid dysfunction, characterized by hypothyroidism or transient thyroid suppression have been reported following iodinated contrast media administration in pediatric patients, including term and preterm neonates. Some patients were treated for hypothyroidism. After exposure to iodinated contrast media, individualize thyroid function monitoring in pediatric patients 0 to 3 years of age based on underlying risk factors, especially in term and preterm neonates [*see Warnings and Precautions (5.9) and Adverse Reactions (6.2)*].

## **8.5 Geriatric Use**

In clinical studies of OMNIPAQUE for CT, 52/299 (17%) of patients were 70 and over. No overall differences in safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In general, dose selection for an elderly patient should be cautious usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

## **10 OVERDOSAGE**

### **10.1 Intravascular Administration**

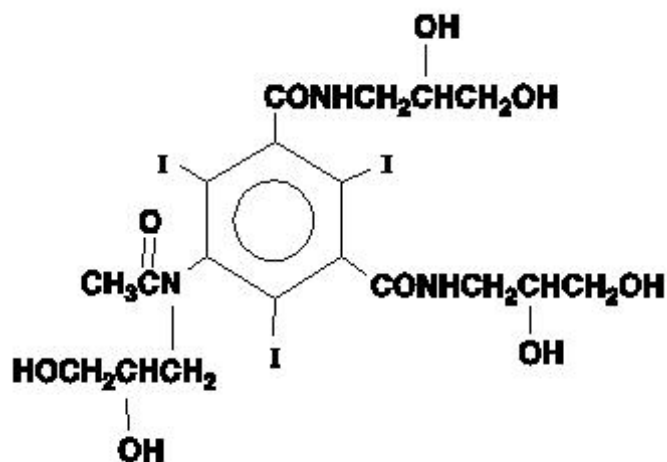
The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular systems. The symptoms included: cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma, and cardiac arrest. Treatment of an overdosage is directed toward the support of all vital functions, and prompt institution of symptomatic therapy. Iohexol displays a low affinity for serum or plasma proteins and is poorly bound to serum albumin and can be dialyzed.

## 11 DESCRIPTION

### 11.1 Chemical Characteristics

OMNIPAQUE (iohexol) injection is a nonionic, x-ray or radiographic contrast medium for intrathecal, intravenous, oral, rectal and body cavity use. OMNIPAQUE oral solution is for oral use only.

OMNIPAQUE injection and OMNIPAQUE oral solution are both provided as sterile, pyrogen-free and gluten-free solutions. OMNIPAQUE injection and OMNIPAQUE oral solution are colorless to pale yellow solutions. The chemical name of iohexol is Bis(2,3-dihydroxypropyl)-5-[ *N*-(2,3-dihydroxypropyl)-acetamido]-2,4,6- triiodoisophthalamide with a molecular weight of 821.14 (iodine content 46.36%). Iohexol has the following structural formula:



OMNIPAQUE injection is available in five strengths:

- OMNIPAQUE 140 mg iodine/mL (302 mg of iohexol/mL): Each mL contains 140 mg organically bound iodine, 1.21 mg tromethamine and 0.1 mg edetate calcium disodium
- OMNIPAQUE 180 mg iodine/mL (388 mg of iohexol/mL): Each mL contains 180 mg organically bound iodine, 1.21 mg tromethamine and 0.1 mg edetate calcium disodium
- OMNIPAQUE 240 mg iodine/mL (518 mg of iohexol/mL): Each mL contains 240 mg organically bound iodine, 1.21 mg tromethamine and 0.1 mg edetate calcium disodium
- OMNIPAQUE 300 mg iodine/mL (647 mg of iohexol/mL): Each mL contains 300 mg organically bound iodine, 1.21 mg tromethamine and 0.1 mg edetate calcium disodium
- OMNIPAQUE 350 mg iodine/mL (755 mg of iohexol/mL): Each mL contains 350 mg organically bound iodine, 1.21 mg tromethamine and 0.1 mg edetate calcium disodium

OMNIPAQUE oral solution is available in two strengths:

- OMNIPAQUE oral solution 9 mg iodine/mL (19 mg of iohexol/mL): Each mL contains 9 mg organically bound iodine, 1.21 mg tromethamine and 0.1 mg edetate calcium disodium
- OMNIPAQUE oral solution 12 mg iodine/mL (26 mg of iohexol/mL): Each mL contains 12 mg organically bound iodine, 1.21 mg tromethamine and 0.1 mg edetate calcium disodium



disodium

The pH is adjusted between 6.8 and 7.7 with hydrochloric acid or sodium hydroxide. OMNIPAQUE injection and OMNIPAQUE oral solution are sterilized by autoclaving and contain no preservatives.

## 11.2 Physical Characteristics

OMNIPAQUE injection and OMNIPAQUE oral solution have the following physical properties:

Presentation	Concentration (mg iodine/mL)	Osmolality * (mOsmol/kg water)	Absolute Viscosity (cP)		Specific Gravity
			20°C	37°C	
OMNIPAQUE 140	140	322	2.3	1.5	1.164
OMNIPAQUE 180	180	408	3.1	2.0	1.209
OMNIPAQUE 240	240	520	5.8	3.4	1.280
OMNIPAQUE 300	300	672	11.8	6.3	1.349
OMNIPAQUE 350	350	844	20.4	10.4	1.406
OMNIPAQUE oral solution 9	9	38	1.1	0.8	1.011
OMNIPAQUE oral solution 12	12	45	1.1	0.8	1.014

\* By vapor-pressure osmometry.

OMNIPAQUE 140, OMNIPAQUE 180, OMNIPAQUE 240, OMNIPAQUE 300, and OMNIPAQUE 350 have osmolalities from approximately 1.1 to 3.0 times that of plasma (285 mOsmol/kg water) or cerebrospinal fluid (301 mOsmol/kg water) as shown in the above table and are hypertonic under conditions of use.

OMNIPAQUE oral solution 9 and OMNIPAQUE oral solution 12 are hypotonic under conditions of use (see table above).

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The iodine atoms in iohexol provide attenuation of X-rays in direct proportion to the concentration of iohexol. Since concentration changes over time, iohexol provides time-dependent image contrast which may assist in visualizing body structures.

### 12.2 Pharmacodynamics

#### Intrathecal Administration

The initial concentration and volume of the contrast medium, in conjunction with patient manipulation and the volume of cerebrospinal fluid (CSF) into which the contrast medium is placed, will determine the extent of the contrast that can be achieved. Following intrathecal injection in conventional radiography, OMNIPAQUE 180, 240, and 300 will continue to provide contrast for at least 30 minutes. Slow diffusion of iohexol takes place throughout the CSF with subsequent absorption into the bloodstream. At approximately 1 hour following injection, contrast will no longer be sufficient for conventional myelography.

After administration into the lumbar subarachnoid space, computerized tomography shows the presence of contrast medium in the thoracic region in about 1 hour, in the cervical region in about 2 hours, and in the basal cisterns in 3 to 4 hours.

#### Intravascular Administration

Following intravascular administration of OMNIPAQUE, the degree of contrast enhancement is directly related to the iodine concentration of an administered dose; peak iodine blood concentrations occur immediately (15 seconds to 120 seconds) following rapid intravenous injection. The time to maximum contrast enhancement can vary, depending on the organ, from the time that peak blood iodine concentrations are reached to one hour after intravenous bolus administration. When a delay between peak blood iodine concentrations and peak contrast is present, it suggests that radiographic contrast enhancement is at least in part dependent on the accumulation of iodine containing agent within the lesion and outside the blood pool.

#### Oral Administration

Orally administered OMNIPAQUE produces visualization of the gastrointestinal tract. Less than 1% of orally administered iohexol is recovered in the urine, suggesting minimal amounts are absorbed from the normal gastrointestinal tract. This amount may increase in the presence of bowel perforation or bowel obstruction.

#### Intraarticular Administration

Visualization of the joint spaces can be accomplished by direct injection of contrast medium. For intraarticular cavities, the injected iohexol is absorbed into the surrounding tissue and subsequently absorbed into systemic circulation.

#### Body Cavity Administration

For most body cavities, the injected iohexol is absorbed into the surrounding tissue and subsequently absorbed into systemic circulation. Examinations of the uterus (hysterosalpingography) and bladder (voiding cystourethrography) involve the almost immediate drainage of contrast medium from the cavity upon conclusion of the radiographic procedure.

### **12.3 Pharmacokinetics**

Following the intravenous administration of iohexol (between 500 mg iodine/kg to 1500 mg iodine/kg) to 16 adult human subjects, apparent first-order terminal elimination half-life was 12.6 hrs and total body clearance was 131 (98 to 165) mL/min. Clearance was not dose dependent.

#### Absorption

As evidenced by the amount recovered in urine, <1% of orally administered iohexol is

absorbed from the normal gastrointestinal tract. This amount may increase in the presence of bowel perforation or bowel obstruction.

#### Distribution

In 16 adult subjects (receiving between 500 mg iodine/kg to 1500 mg iodine/kg intravenous iohexol) the plasma volume of distribution was 165 (108 to 219) mL/kg.

In five adult patients receiving 16 mL to 18 mL of OMNIPAQUE (180 mg iodine/mL) by lumbar intrathecal injection the plasma volume of distribution was 559 (350 to 849) mL/kg.

#### Elimination

##### *Metabolism*

No significant metabolism, deiodination or biotransformation occurs.

##### *Excretion*

Following intravascular or intrathecal administration, iohexol is excreted unchanged by glomerular filtration. Approximately 90% of the intravenously injected iohexol dose is excreted within the first 24 hours. Following intravascular administration, peak urine concentration occurs in the first hour after injection.

## **13 NONCLINICAL TOXICOLOGY**

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

Long-term animal studies have not been performed with iohexol to evaluate carcinogenic potential. Iohexol was not genotoxic in a series of studies, including the Ames test, the mouse lymphoma TK locus forward mutation assay, and a mouse micronucleus assay. Iohexol did not impair the fertility of male or female rats when repeatedly administered at intravenous dosages up to 4 g iodine/kg.

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

### **16.1 How Supplied**

<b>Volume/Concentration</b>	<b>Configuration</b>	<b>NDC</b>
<b>OMNIPAQUE 140 (140 mg iodine/mL) - Boxes of 10</b>		
50 mL	+ PLUSPAK™ (polymer bottle)	0407-1401-52
<b>OMNIPAQUE 180 (180 mg iodine/mL) - Boxes of 10</b>		
10 mL	Glass Vial	0407-1411-10
<b>OMNIPAQUE 240 (240 mg iodine/mL) - Boxes of 10</b>		
10 mL	Glass Vial	0407-1412-10
20 mL	Glass Vial	0407-1412-20
50 mL	+ PLUSPAK™ (polymer bottle)	0407-1412-30
100 mL	+ PLUSPAK™ (polymer bottle)	0407-1412-33

<b>OMNIPAQUE 300 (300 mg iodine/mL) - Boxes of 10</b>		
10 mL	Glass Vial	0407-1413-10
30 mL fill in 50 mL	+ <i>PLUSPAK</i> <sup>™</sup> (polymer bottle)	0407-1413-59
50 mL	+ <i>PLUSPAK</i> <sup>™</sup> (polymer bottle)	0407-1413-61
100 mL	+ <i>PLUSPAK</i> <sup>™</sup> (polymer bottle)	0407-1413-63
125 mL fill in 150 mL	Glass Bottle	0407-1413-53
150 mL fill in 200 mL	+ <i>PLUSPAK</i> <sup>™</sup> (polymer bottle)	0407-1413-65
<b>OMNIPAQUE 350 (350 mg iodine/mL) - Boxes of 10</b>		
50 mL	+ <i>PLUSPAK</i> <sup>™</sup> (polymer bottle)	0407-1414-89
75 mL fill in 100 mL	+ <i>PLUSPAK</i> <sup>™</sup> (polymer bottle)	0407-1414-90
100 mL	+ <i>PLUSPAK</i> <sup>™</sup> (polymer bottle)	0407-1414-91
125 mL fill in 150 mL	Glass Bottle	0407-1414-76
150 mL fill in 200 mL	+ <i>PLUSPAK</i> <sup>™</sup> (polymer bottle)	0407-1414-93
200 mL	+ <i>PLUSPAK</i> <sup>™</sup> (polymer bottle)	0407-1414-94
<b>OMNIPAQUE Oral Solution 9 (9 mg iodine/mL) - Boxes of 10</b>		
500 mL	+ <i>PLUSPAK</i> <sup>™</sup> (polymer bottle)	0407-1415-09
<b>OMNIPAQUE Oral Solution 12 (12 mg iodine/mL) - Boxes of 10</b>		
500 mL	+ <i>PLUSPAK</i> <sup>™</sup> (polymer bottle)	0407-1416-12

The container closure system components (bottle, vial, stopper and cap) of OMNIPAQUE injection and OMNIPAQUE oral solution are not made with natural rubber latex.

## 16.2 Storage and Handling

Protect OMNIPAQUE glass vials and bottles and + *PLUSPAK*<sup>™</sup> polymer bottles from light. Do not freeze. Discard any product that is inadvertently frozen, as freezing may compromise the closure integrity of the immediate container.

### OMNIPAQUE Injection 140, 180, 240, 300 and 350

Store at controlled room temperature, 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. May be stored in a contrast media warmer for up to one month at 36° to 38°C (96.8° to 100.4°F).

### OMNIPAQUE Oral Solution 9 and 12

Store between 0° and 30°C (32° to 86°F).

## 17 PATIENT COUNSELING INFORMATION

### Hypersensitivity Reactions

Advise the patient concerning the risk of hypersensitivity reactions that can occur both during and after OMNIPAQUE administration. Advise the patient to report any signs or symptoms of hypersensitivity reactions during the procedure and to seek immediate medical attention for any signs or symptoms experienced after discharge [see *Warnings and Precautions* (5.3)]

Advise patients to inform their physician if they develop a rash after receiving OMNIPAQUE [see *Warnings and Precautions* (5.12)].

### Contrast-Induced Acute Kidney Injury

Advise the patient concerning appropriate hydration to decrease the risk of contrast-induced acute kidney injury [see *Warnings and Precautions* (5.4)] .

### Extravasation

If extravasation occurs during injection, advise patients to seek medical care for progression of symptoms [see *Warnings and Precautions* (5.7)].

### Lactation

Advise a lactating woman that interruption of breastfeeding is not necessary. However, to avoid any exposure, a lactating woman may consider pumping and discarding breast milk for 10 hours after OMNIPAQUE administration [ see *Use in Specific Populations* (8.2)] .

### Thyroid Dysfunction

Advise parents/caregivers about the risk of developing thyroid dysfunction after OMNIPAQUE administration. Advise parents/caregivers about when to seek medical care for their child to monitor for thyroid function [see *Warnings and Precautions* (5.9)].

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### **Lidocaine HCl Injection, USP**

For Infiltration and Nerve Block Including Caudal and Epidural Use.

Preservative-Free

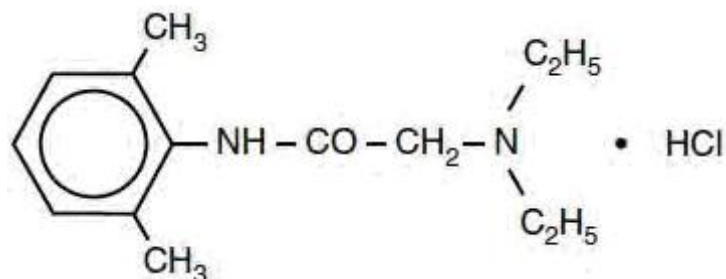
### **Rx only**

### **DESCRIPTION**

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

Lidocaine hydrochloride injection, USP contains lidocaine hydrochloride, which is

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



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

## CLINICAL PHARMACOLOGY

### ***Mechanism of Action***

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

### ***Hemodynamics***

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

### ***Pharmacokinetics and Metabolism***

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

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

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

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

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

Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lidocaine hydrochloride required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6 mcg free base per mL. In the rhesus monkey arterial blood levels of 18 to 21 mcg/mL have been shown to be threshold for convulsive activity.

## **INDICATIONS AND USAGE**

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

## **CONTRAINDICATIONS**

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

## **WARNINGS**

LIDOCAINE HYDROCHLORIDE INJECTION FOR INFILTRATION AND NERVE BLOCK SHOULD BE EMPLOYED ONLY BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES THAT MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED AND THEN ONLY AFTER ENSURING THE *IMMEDIATE* AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY EQUIPMENT AND THE PERSONNEL NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES (see also **ADVERSE REACTIONS** and **PRECAUTIONS**). DELAY IN PROPER MANAGEMENT OF DOSE-

RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

### ***Methemoglobinemia***

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

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

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

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

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

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

## **PRECAUTIONS**

### ***General***



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

Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use (see **WARNINGS** and **ADVERSE REACTIONS**). The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Syringe aspirations should also be performed before and during each supplemental injection when using indwelling catheter techniques. During the administration of epidural anesthesia, it is recommended that a test dose be administered initially and that the patient be monitored for central nervous system toxicity and cardiovascular toxicity, as well as for signs of unintended intrathecal administration, before proceeding. When clinical conditions permit, consideration should be given to employing local anesthetic solutions that contain epinephrine for the test dose because circulatory changes compatible with epinephrine may also serve as a warning sign of unintended intravascular injection. An intravascular injection is still possible even if aspirations for blood are negative. Repeated doses of lidocaine hydrochloride may cause significant increases in blood levels with each repeated dose because of slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical condition. Lidocaine hydrochloride should also be used with caution in patients with severe shock or heart block.

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

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

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

Since amide-type local anesthetics are metabolized by the liver, lidocaine hydrochloride injection should be used with caution in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations. Lidocaine hydrochloride injection should also be used with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.

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

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

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

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

Small doses of local anesthetics injected into the head and neck area, including retrobulbar, dental and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded (see **DOSAGE AND ADMINISTRATION**).

### ***Information for Patients***

When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body, following proper administration of epidural anesthesia.

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

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

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

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

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

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

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

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

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

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

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

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

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

### ***Pregnancy***

#### **Teratogenic Effects**

Reproduction studies have been performed in rats at doses up to 6.6 times the human dose and have revealed no evidence of harm to the fetus caused by lidocaine hydrochloride. There are, however, no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response.

General consideration should be given to this fact before administering lidocaine hydrochloride to women of childbearing potential, especially during early pregnancy when maximum organogenesis takes place.

### ***Labor and Delivery***

Local anesthetics rapidly cross the placenta and when used for epidural, paracervical, pudendal or caudal block anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity (see **CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism**). The potential for toxicity depends upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure.

The fetal heart rate also should be monitored continuously, and electronic fetal monitoring is highly advisable.

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

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

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

sides.

### ***Nursing Mothers***

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

### ***Pediatric Use***

Dosages in children should be reduced, commensurate with age, body weight and physical condition, see **DOSAGE AND ADMINISTRATION**.

## **ADVERSE REACTIONS**

### ***Systemic***

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

#### ***Central Nervous System***

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

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

#### ***Cardiovascular System***

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

### ***Allergic***

Allergic reactions are characterized by cutaneous lesions, urticaria, edema or anaphylactoid reactions. Allergic reactions may occur as a result of sensitivity to local anesthetic agents. Allergic reactions, including anaphylactic reactions, may occur as a result of sensitivity to lidocaine, but are infrequent. If allergic reactions do occur, they

should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

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

### ***Neurologic***

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

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

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

### ***Hematologic***

Methemoglobinemia.

## **OVERDOSAGE**

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

### ***Management of Local Anesthetic Emergencies***

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

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

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

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

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

The oral LD<sub>50</sub> of lidocaine hydrochloride in non-fasted female rats is 459 (346 to 773) mg/kg (as the salt) and 214 (159 to 324) mg/kg (as the salt) in fasted female rats.

## **DOSAGE AND ADMINISTRATION**

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

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

These recommended doses serve only as a guide to the amount of anesthetic required for most routine procedures. The actual volumes and concentrations to be used depend on a number of factors such as type and extent of surgical procedure, depth of anesthesia and degree of muscular relaxation required, duration of anesthesia required,

and the physical condition of the patient. In all cases the lowest concentration and smallest dose that will produce the desired result should be given. Dosages should be reduced for children and for the elderly and debilitated patients and patients with cardiac and/or liver disease.

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

### ***Epidural Anesthesia***

For epidural anesthesia the following dosage form of lidocaine hydrochloride injection is recommended:

1% without epinephrine 30 mL single dose vials

Although this solution is intended specifically for epidural anesthesia, it may also be used for infiltration and peripheral nerve block, provided it is employed as a single dose unit.

This solution contains no bacteriostatic agent.

In epidural anesthesia, the dosage varies with the number of dermatomes to be anesthetized (generally 2 to 3 mL of the indicated concentration per dermatome).

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

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



administered.

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

## MAXIMUM RECOMMENDED DOSAGES

### **Adults**

For normal healthy adults, the maximum individual dose should not exceed 4.5 mg/kg (2 mg/lb) of body weight, and in general it is recommended that the maximum total dose does not exceed 300 mg. For continuous epidural or caudal anesthesia, the maximum recommended dosage should not be administered at intervals of less than 90 minutes. When continuous lumbar or caudal epidural anesthesia is used for non-obstetrical procedures, more drug may be administered if required to produce adequate anesthesia.

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

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

### **Children**

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

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

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. Do not use if solution is discolored or contains a precipitate.

**Table 1: Recommended Dosages**

	<b>Lidocaine Hydrochloride Injection</b>
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Procedure	(without epinephrine)		
	Conc (%)	Vol (mL)	Total Dose (mg)
Infiltration			
Percutaneous	0.5 or 1	1 to 60	5 to 300
Intravenous regional	0.5	10 to 60	50 to 300
Peripheral Nerve Blocks, e.g.,			
Brachial	1.5	15 to 20	225 to 300
Dental	2	1 to 5	20 to 100
Intercostal	1	3	30
Paravertebral	1	3 to 5	30 to 50
Pudendal (each side)	1	10	100
Paracervical			
Obstetrical analgesia (each side)	1	10	100
Sympathetic Nerve Blocks, e.g.,			
Cervical (stellate ganglion)	1	5	50
Lumbar	1	5 to 10	50 to 100
Central Neural Blocks			
Epidural*			
Thoracic	1	20 to 30	200 to 300
Lumbar			
Analgesia	1	25 to 30	250 to 300
Anesthesia	1.5	15 to 20	225 to 300
	2	10 to 15	200 to 300
Caudal			
Obstetrical analgesia	1	20 to 30	200 to 300
Surgical anesthesia	1.5	15 to 20	225 to 300

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

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

## STERILIZATION, STORAGE AND TECHNICAL PROCEDURES

Disinfecting agents containing heavy metals, which cause release of respective ions (mercury, zinc, copper, etc.) should not be used for skin or mucous membrane disinfection as they have been related to incidents of swelling and edema.

## HOW SUPPLIED

Lidocaine Hydrochloride Injection, USP is supplied as follows:

Lidocaine Hydrochloride Injection USP, 2% (20 mg/mL)

2 mL Single Dose Vials in a Carton of 10 NDC 55150-164-02

## Sterile, Nonpyrogenic

Discard unused portion

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

The vial stopper is not made with natural rubber latex.

Distributed by:

**AuroMedics Pharma LLC**

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

Manufactured by:

**Aurobindo Pharma Limited**

Hyderabad - 500038  
India

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**Triamcinolone Acetonide Injectable Suspension, USP**

**NOT FOR USE IN NEONATES  
CONTAINS BENZYL ALCOHOL**

**For Intramuscular or Intra-articular Use Only**

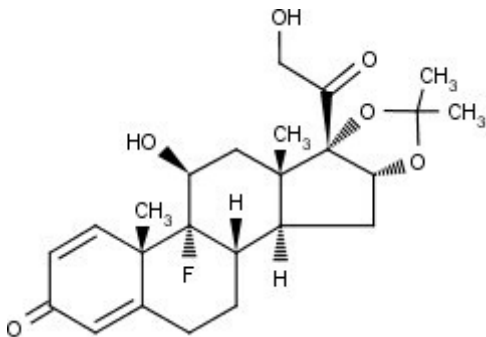
**NOT FOR INTRAVENOUS, INTRADERMAL, INTRAOCULAR, EPIDURAL, OR  
INTRATHECAL USE**

## DESCRIPTION

Triamcinolone acetonide injectable suspension, USP is a synthetic glucocorticoid corticosteroid with anti-inflammatory action. THIS FORMULATION IS SUITABLE FOR INTRAMUSCULAR AND INTRA-ARTICULAR USE ONLY. THIS FORMULATION IS NOT FOR INTRADERMAL INJECTION.

Each mL of the sterile aqueous suspension provides 40 mg triamcinolone acetonide, USP, with 0.65% sodium chloride for isotonicity, 0.99% (w/v) benzyl alcohol as a preservative, 0.75% carboxymethylcellulose sodium, and 0.04% polysorbate 80 in an aqueous suspension. Sodium hydroxide or hydrochloric acid may be present to adjust pH to 5.0 to 7.5. At the time of manufacture, the air in the container is replaced by nitrogen.

The chemical name for triamcinolone acetonide is 9-Fluoro-11 $\beta$ ,16 $\alpha$ ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone. Its structural formula is:



MW 434.50

Triamcinolone acetonide, USP occurs as a white to cream-colored, crystalline powder having not more than a slight odor and is practically insoluble in water and very soluble in alcohol.

## CLINICAL PHARMACOLOGY

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

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

Triamcinolone acetonide injectable suspension has an extended duration of effect which may be sustained over a period of several weeks. Studies indicate that following a single intramuscular dose of 60 mg to 100 mg of triamcinolone acetonide, adrenal suppression occurs within 24 to 48 hours and then gradually returns to normal, usually in 30 to 40 days. This finding correlates closely with the extended duration of therapeutic action achieved with the drug.

## INDICATIONS AND USAGE

### Intramuscular

Where oral therapy is not feasible, injectable corticosteroid therapy, including triamcinolone acetonide injectable suspension is indicated **for intramuscular use** as follows:

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

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

*Endocrine disorders:* 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), congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsuppurative thyroiditis.

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

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

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

*Neoplastic diseases:*For the palliative management of leukemias and lymphomas.

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

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

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

*Respiratory diseases:*Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.

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

### **Intra-Articular**

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

## **CONTRAINDICATIONS**

Triamcinolone acetonide injectable suspension is contraindicated in patients who are hypersensitive to any components of this product (see **WARNINGS: General**).

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

## **WARNINGS**

### **Serious Neurologic Adverse Reactions with Epidural Administration**

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

### **General**

Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of

benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administered. The amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (see **PRECAUTIONS: Pediatric Use**).

Rare instances of anaphylaxis have occurred in patients receiving corticosteroid therapy (see **ADVERSE REACTIONS**). Cases of serious anaphylaxis, including death, have been reported in individuals receiving triamcinolone acetonide injection, regardless of the route of administration.

Because triamcinolone acetonide injectable suspension is a suspension, it should **not** be administered intravenously.

Unless a **deep** intramuscular injection is given, local atrophy is likely to occur (for recommendations on injection techniques, see **DOSAGE AND ADMINISTRATION**). Due to the significantly higher incidence of local atrophy when the material is injected into the deltoid area, this injection site should be avoided in favor of the gluteal area.

Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation. Triamcinolone acetonide injectable suspension is a long-acting preparation, and is not suitable for use in acute stress situations. To avoid drug-induced adrenal insufficiency, supportive dosage may be required in times of stress (such as trauma, surgery, or severe illness) both during treatment with triamcinolone acetonide injectable suspension and for a year afterwards.

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

### **Cardio-Renal**

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

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

### **Endocrine**

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

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and

increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

## **Infections**

### **General**

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

### **Fungal Infections**

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

### **Special Pathogens**

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

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

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

Corticosteroids should not be used in cerebral malaria.

### **Tuberculosis**

The use of corticosteroids in patients with 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 anti-tuberculosis 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.

### **Vaccination**

**Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or**

**inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted.** Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

## **Viral Infections**

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

## **Neurologic**

Epidural and intrathecal administration of this product is not recommended. Reports of serious medical events, including death, have been associated with epidural and intrathecal routes of corticosteroid administration (see **ADVERSE REACTIONS: Gastrointestinal and Neurologic/Psychiatric**).

## **Ophthalmic**

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 bacteria, fungi, or viruses. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should not be used in active ocular herpes simplex.

Adequate studies to demonstrate the safety of triamcinolone acetonide injectable suspension use by intratubinal, subconjunctival, sub-Tenons, retrobulbar and intraocular (intravitreal) injections have not been performed. Endophthalmitis, eye inflammation, increased intraocular pressure and visual disturbances including vision loss have been reported with intravitreal administration. Administration of triamcinolone acetonide injectable suspension intraocularly or into the nasal turbinates is not recommended.

Intraocular injection of corticosteroid formulations containing benzyl alcohol, such as triamcinolone acetonide injectable suspension is not recommended because of potential toxicity from the benzyl alcohol.

## **PRECAUTIONS**

### **General**

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

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

Since complications of treatment with glucocorticoids are dependent on the size of the



dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

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

### **Cardio-Renal**

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

### **Endocrine**

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

### **Gastrointestinal**

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

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

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

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

Intra-articularly injected corticosteroids may be systemically absorbed.

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

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

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

Corticosteroid injection into unstable joints is generally not recommended.

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

### **Musculoskeletal**

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (i.e. decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the

development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e. postmenopausal women) before initiating corticosteroid therapy.

## **Neuro-Psychiatric**

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

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

Psychiatric 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.

## **Ophthalmic**

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

## **Information for Patients**

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

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

## **Drug Interactions**

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

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

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

*Anticholinesterases:* Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible,

anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

*Anticoagulants, oral:* Co-administration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

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

*Antitubercular drugs:* Serum concentrations of isoniazid may be decreased.

*Cholestyramine:* Cholestyramine may increase the clearance of corticosteroids.

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

*CYP 3A4 inhibitors:* Triamcinolone acetonide is a substrate of CYP3A4. Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects. Co-administration of other strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin, cobicistat-containing products) with triamcinolone acetonide injectable suspension may cause increased plasma concentration of triamcinolone leading to adverse reactions (see **ADVERSE REACTIONS**). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving triamcinolone acetonide and strong CYP3A4 inhibitors (e.g., ritonavir) (see **WARNINGS, Endocrine** and **PRECAUTIONS, Endocrine**). Consider the benefit-risk of concomitant use and monitor for systemic corticosteroid side effects.

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

*Estrogens, including oral contraceptives:* Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

*Hepatic enzyme inducers (e.g., barbiturates, phenytoin, carbamazepine, rifampin):* Drugs which induce hepatic microsomal drug metabolizing enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

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

*Skin tests:* Corticosteroids may suppress reactions to skin tests.

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

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

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

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

## **Pregnancy**

### **Teratogenic Effects**

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

## **Nursing Mothers**

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

## **Pediatric Use**

This product contains benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The “gasping syndrome” (characterized by central nervous system depression, metabolic acidosis, gasping respirations and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages > 99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome,” the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

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

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

### **Geriatric Use**

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

### **ADVERSE REACTIONS**

**(listed alphabetically under each subsection)**

The following adverse reactions may be associated with corticosteroid therapy:

*Allergic reactions:* Anaphylaxis including death, angioedema.

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

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

*Endocrine:* Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, postmenopausal vaginal hemorrhage, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

*Fluid and electrolyte disturbances:* Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

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

*Metabolic:* Negative nitrogen balance due to protein catabolism.

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

*Neurologic/Psychiatric:* Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychiatric disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia and sensory disturbances have occurred after intrathecal administration. Spinal cord infarction, paraplegia, quadriplegia, cortical blindness and stroke (including brainstem) have been reported after epidural administration of corticosteroids (see **WARNINGS: Serious Neurologic Adverse Reactions with Epidural Administration** and **WARNINGS: Neurologic**).

*Ophthalmic:* Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, rare instances of blindness associated with periocular injections.

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

**To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

## **OVERDOSAGE**

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

## **DOSAGE AND ADMINISTRATION**

### **General**

**NOTE: CONTAINS BENZYL ALCOHOL (see PRECAUTIONS).**

The initial dose of triamcinolone acetonide injectable suspension may vary from 2.5 mg to 100 mg per day depending on the specific disease entity being treated (see **Dosage** section below). However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

**IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER**

**TREATMENT AND THE RESPONSE OF THE PATIENT.**After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

## **Dosage**

### **SYSTEMIC**

The suggested initial dose is 60 mg, **injected deeply into the gluteal muscle.** Atrophy of subcutaneous fat may occur if the injection is not properly given. Dosage is usually adjusted within the range of 40 mg to 80 mg, depending upon patient response and duration of relief. However, some patients may be well controlled on doses as low as 20 mg or less.

Hay fever or pollen asthma: Patients with hay fever or pollen asthma who are not responding to pollen administration and other conventional therapy may obtain a remission of symptoms lasting throughout the pollen season after a single injection of 40 mg to 100 mg.

In the treatment of acute exacerbations of multiple sclerosis, daily doses of 160 mg of triamcinolone for a week followed by 64 mg every other day for one month are recommended (see **PRECAUTIONS: Neuro-Psychiatric**).

In pediatric patients, the initial dose of triamcinolone may vary depending on the specific disease entity being treated. The range of initial doses is 0.11 to 1.6 mg/kg/day in 3 or 4 divided doses (3.2 to 48 mg/m<sup>2</sup>bsa/day).

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

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

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

### **LOCAL**

**Intra-articular administration:**A single local injection of triamcinolone acetonide is frequently sufficient, but several injections may be needed for adequate relief of symptoms.

**Initial dose:** 2.5 mg to 5 mg for smaller joints and from 5 mg to 15 mg for larger joints, depending on the specific disease entity being treated. For adults, doses up to 10 mg for smaller areas and up to 40 mg for larger areas have usually been sufficient. Single injections into several joints, up to a total of 80 mg, have been given.

## **Administration**

### **GENERAL**

**STRICT ASEPTIC TECHNIQUE IS MANDATORY.** The vial should be shaken before use to ensure a uniform suspension. Prior to withdrawal, the suspension should be inspected for clumping or granular appearance (agglomeration). An agglomerated product results from exposure to freezing temperatures and should not be used. After withdrawal, triamcinolone acetonide injectable suspension should be injected without delay to prevent settling in the syringe. Careful technique should be employed to avoid the possibility of entering a blood vessel or introducing infection.

### **SYSTEMIC**

For systemic therapy, injection should be made **deeply into the gluteal muscle** (see **WARNINGS**). For adults, a minimum needle length of 1½ inches is recommended. In obese patients, a longer needle may be required. Use alternative sites for subsequent injections.

### **LOCAL**

For treatment of joints, the usual intra-articular injection technique should be followed. If an excessive amount of synovial fluid is present in the joint, some, but not all, should be aspirated to aid in the relief of pain and to prevent undue dilution of the steroid.

With intra-articular administration, prior use of a local anesthetic may often be desirable. Care should be taken with this kind of injection, particularly in the deltoid region, to avoid injecting the suspension into the tissues surrounding the site, since this may lead to tissue atrophy.

In treating acute nonspecific tenosynovitis, care should be taken to ensure that the injection of the corticosteroid is made into the tendon sheath rather than the tendon substance. Epicondylitis may be treated by infiltrating the preparation into the area of greatest tenderness.

### **HOW SUPPLIED**

Triamcinolone Acetonide Injectable Suspension, USP is supplied in vials providing 40 mg triamcinolone acetonide per mL.

#### **40 mg/mL, 1 mL**

1 mL single-dose vial: NDC 70121-1049-1

25 single-dose vials in 1 carton: NDC 70121-1049-5

### **Storage**

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from temperatures below 20°C (68°F). Store vial in carton to protect from light. Store vial upright.

Discard unused portions of single-dose vials.



Manufactured by:

**Amneal Pharmaceuticals Pvt. Ltd.**

**Parenteral Unit**

Ahmedabad 382213, INDIA

Distributed by:

**Amneal Pharmaceuticals LLC**

Bridgewater, NJ 08807

Rev. 08-2020-05

## **ChloraPrep One-Step**

### ***Active ingredients***

Chlorhexidine gluconate 2% w/v

Isopropyl alcohol 70% v/v

### ***Purposes***

Antiseptic

Antiseptic

### **Use**

for the preparation of the patient's skin prior to surgery. Helps to reduce bacteria that potentially can cause skin infection.

### ***Warnings***

**For external use only. Flammable, keep away from fire or flame. To reduce risk of fire, PREP CAREFULLY:**

- solution contains alcohol and gives off **flammable vapors**
- avoid getting solution into hairy areas. Hair may take up to 1 hour to dry. **Wet hair is flammable.**
- do not drape or use ignition source (e.g., cautery, laser) until solution is completely dry (**minimum of 3 minutes on hairless skin; up to 1 hour in hair**)
- do not allow solution to pool
- remove wet materials from prep area

### **Allergy alert:**

This product may cause a severe allergic reaction. Symptoms may include:

- wheezing/difficulty breathing • shock • facial swelling • hives • rash

If an allergic reaction occurs, stop use and seek medical help right away.

### **Do not use**

- on patients allergic to chlorhexidine gluconate or any other ingredient in this product
- for lumbar puncture or in contact with the meninges
- on open skin wounds or as a general skin cleanser

### **When using this product**

keep out of eyes, ears, and mouth. May cause serious or permanent injury if permitted to enter and remain. If contact occurs, rinse with cold water right away and contact a doctor.

### **Stop use and ask a doctor if**

irritation, sensitization, or allergic reaction occurs. These may be signs of a serious condition.

### **Keep out of reach of children.**

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

### ***Directions***

- use with care in premature infants or infants under 2 months of age.

These products may cause irritation or chemical burns. • use in a well ventilated area

- maximal treatment area for one applicator is approximately **4 in. x 5 in. (130 cm<sup>2</sup>)**
- remove applicator from package; do not touch sponge • hold the applicator with the sponge down. Pinch wings **only once** to activate the ampule and release the antiseptic.

- wet the sponge by pressing and releasing the sponge against the treatment area until liquid

is visible on the skin • completely wet the treatment area with antiseptic • **dry surgical**

**sites**(e.g., abdomen or arm): use gentle repeated back-and-forth strokes of the sponge for

approximately 30 seconds Allow solution to air dry for approximately 30 seconds. Do not blot

or wipe away. • **moist surgical sites**(e.g., inguinal fold): use gentle repeated back-and-forth

strokes for approximately 2 minutes. • Allow solution to air dry for approximately 1 minute. Do not blot or wipe away. • **if using an ignition source, allow the solution to**

**completely dry(minimum of 3 minutes on hairless skin; up to 1 hour in hair).**Do not blot

or wipe away. • discard the applicator after a single use along with any portion of the solution

not required to cover the prep area. It is not necessary to use the entire amount available.

### **Other Information**

• store between 15-30 °C (59-86 °F) • avoid freezing and excessive heat above 40 °C (104 °F)

### **Inactive Ingredient**

USP purified water

### **Questions?**

[www.chloraprep.com](http://www.chloraprep.com) • call **1-800-523-0502**(M-F 8 a.m.-5 p.m. CST)

## **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: 76420-737-01****Rx Only****MLK F4-C Kit™****Kit Contains**

- 1 Bupivacaine HCl 0.5% Single Dose Vial (10mL)
- 1 Lidocaine HCL Injection, USP 2% (2mL)
- 1 Triamcinolone Acetonide Injectable Suspension, USP 40 mg/mL (1mL)
- 1 Omnipaque™ (iohexol) Injection 240mg/mL Single Dose Bottle (10mL)
- 1 BD Chloraprep™ Clear (3mL Applicator)
- 4 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

**NDC: 76420-737-01****Rx Only**

**MLK F4-C Kit™**

1	<b>Kit Contains</b>
1	Bupivacaine HCl 0.5% Single Dose Vial (10mL)
1	Lidocaine HCl Injection, USP 2% (2mL)
1	Triamcinolone Acetonide Injectable Suspension, USP 40 mg/mL (1mL)
1	Omnipaque™ (iohexol) Injection 240mg/mL Single Dose Bottle (10mL)
1	BD Chloraprep™ Clear (3mL Applicator)
4	Isopropyl Alcohol 70% Prep Pads
1	Pair Nitrile Powder Free Sterile Gloves (M)
1	Drape
1	Adhesive Bandage
5	Non Sterile 4 x 4 Gauze
	Needles and Syringes Not Included
	1 Dose
	Single Use Only

Distributed by

**Enovachem™**  
PHARMACEUTICALS  
Torrance, CA 90501

## MLK F4-C

bupivacaine hydrochloride, lidocaine hydrochloride, triamcinolone acetonide, iohexol, isopropyl alcohol, chlorhexidine gluconate kit

### Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:76420-737
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Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:76420-737-01	1 in 1 CARTON; Type 1: Convenience Kit of Co-Package	07/01/2024	

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	4 POUCH	20 mL
Part 2	1 APPLICATOR	3 mL
Part 3	1 VIAL	1 mL
Part 4	1 VIAL, SINGLE-DOSE	2 mL
Part 5	1 VIAL, SINGLE-DOSE	10 mL
Part 6	1 VIAL, GLASS	10 mL

Part 1 of 6

ISOPROPYL ALCOHOL

isopropyl alcohol swab

Product Information

Route of Administration      TOPICAL

Active Ingredient/Active Moiety

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

Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		5 mL in 1 POUCH; Type 0: Not a Combination Product		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
OTC Monograph Drug	M003	01/01/2007	

## Part 2 of 6

### CHLORAPREP ONE-STEP

chlorhexidine gluconate and isopropyl alcohol solution

## Product Information

Item Code (Source)	NDC:54365-400
Route of Administration	TOPICAL

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>CHLORHEXIDINE GLUCONATE</b> (UNII: MOR84MUD8E) (CHLORHEXIDINE - UNII:R4KO0DY52L)	CHLORHEXIDINE GLUCONATE	20 mg in 1 mL
<b>ISOPROPYL ALCOHOL</b> (UNII: ND2M416302) (ISOPROPYL ALCOHOL - UNII:ND2M416302)	ISOPROPYL ALCOHOL	0.7 mL in 1 mL

## Inactive Ingredients

Ingredient Name	Strength
<b>WATER</b> (UNII: 059QF0KO0R)	

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54365-400-32	25 in 1 CARTON		
1		1 in 1 POUCH		
1		3 mL in 1 APPLICATOR; Type 0: Not a Combination Product		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020832	05/24/2019	

## Part 3 of 6

### TRIAMCINOLONE ACETONIDE

triamcinolone acetonide injection, suspension

## Product Information

Item Code (Source)	NDC:70121-1049
Route of Administration	INTRA-ARTICULAR, INTRAMUSCULAR

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TRIAMCINOLONE ACETONIDE (UNII: F446C597KA) (TRIAMCINOLONE ACETONIDE - UNII:F446C597KA)	TRIAMCINOLONE ACETONIDE	40 mg in 1 mL

## Inactive Ingredients

Ingredient Name	Strength
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
BENZYL ALCOHOL (UNII: LKG8494WBH)	
CARBOXYMETHYLCELLULOSE SODIUM (UNII: K679OBS311)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

## Product Characteristics

Color	white (white to cream-color)	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70121-1049-5	25 in 1 CARTON		
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	ANDA207550	12/11/2017	



## LIDOCAINE HYDROCHLORIDE

lidocaine hydrochloride injection, solution

### Product Information

**Item Code (Source)** NDC:55150-164

**Route of Administration** INFILTRATION

### Active Ingredient/Active Moiety

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

### Inactive Ingredients

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

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55150-164-02	10 in 1 CARTON		
1		2 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	ANDA203082	03/14/2013	

## Part 5 of 6

## BUPIVACAINE HYDROCHLORIDE

bupivacaine hydrochloride injection, solution

### Product Information

**Item Code (Source)** NDC:0409-1162

**Route of Administration** EPIDURAL, INFILTRATION, PERINEURAL

**Active Ingredient/Active Moiety**

Ingredient Name	Basis of Strength	Strength
<b>BUPIVACAINE HYDROCHLORIDE</b> (UNII: 7TQO7W3VT8) (BUPIVACAINE - UNII:Y8335394RO)	BUPIVACAINE HYDROCHLORIDE ANHYDROUS	5 mg in 1 mL

**Inactive Ingredients**

Ingredient Name	Strength
<b>SODIUM CHLORIDE</b> (UNII: 451W47IQ8X)	
<b>SODIUM HYDROXIDE</b> (UNII: 55X04QC32I)	
<b>HYDROCHLORIC ACID</b> (UNII: QTT17582CB)	
<b>WATER</b> (UNII: 059QF0KO0R)	

**Packaging**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0409-1162-18	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	ANDA070584	11/22/2005	

**Part 6 of 6****OMNIPAQUE**

iohexol injection, solution

**Product Information**

<b>Item Code (Source)</b>	NDC:0407-1412
<b>Route of Administration</b>	INTRAVENOUS, INTRAVASCULAR, INTRATHECAL, INTRA-ARTICULAR

**Active Ingredient/Active Moiety**

Ingredient Name	Basis of Strength	Strength
<b>IOHEXOL</b> (UNII: 4419T9MX03) (IOHEXOL - UNII:4419T9MX03)	IODINE	240 mg in 1 mL

**Inactive Ingredients**

Ingredient Name	Strength
<b>TROMETHAMINE</b> (UNII: 023C2WHX2V)	1.21 in 1 mL

EDETATE CALCIUM DISODIUM (UNII: 25IH6R4SGF)				
HYDROCHLORIC ACID (UNII: QTT17582CB)				
SODIUM HYDROXIDE (UNII: 55X04QC32I)				
Product Characteristics				
Color	yellow (colorless to pale yellow)			Score
Shape				Size
Flavor				Imprint Code
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0407-1412-10	10 in 1 BOX		
1		10 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA		NDA018956	12/26/1985	
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other			07/01/2024	

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