PHYSICIANS EZ USE M-PRED- methylprednisolone acetate, bupivacaine hydrochloride, povidone-iodine
Asclemed USA, Inc.

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

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, 5.5, 5.7, 5.9)

DOSAGE AND ADMINISTRATION

- Not for intrathecal use. (2.1)
- Avoid use of solutions containing antimicrobial preservatives (i.e., multiple-dose vials) for epidural or caudal anesthesia. (2.1)
- See full prescribing information for:

- Recommended concentrations and dosages of Bupivacaine Hydrochloride Injection according to type of block. (2.2)
- Additional dosage and administration information pertaining to use in epidural anesthesia and use in ophthalmic surgery. (2.3, 2.6)

DOSAGE FORMS AND STRENGTHS

Bupivacaine Hydrochloride Injection, USP are available in following concentrations. See full prescribing information for detailed description of each formulation. (3)

CONTRAINDICATIONS

- Obstetrical paracervical block anesthesia. Its use in this technique has resulted in fetal bradycardia and death. (4)

- Intravenous regional anesthesia (Bier Block). (4)
- Known hypersensitivity to bupivacaine or to any local anesthetic agent of the amide-type or to other components of Bupivacaine Hydrochloride Injection. (4)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and PATIENT COUNSELING INFORMATION.

Revised: 7/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

Cardio-renal
Endocrine
Gastrointestinal
Parenteral Administration
Musculoskeletal
Neuro-psychiatric
Ophthalmic
Information for the Patient
Drug Interactions
Carcinogenesis, Mutagenesis, Impairment of Fertility
Pregnancy: Teratogenic Effects
Nursing Mothers
Pediatric Use
Geriatric Use
B. Administration for Systemic Effect
Storage Conditions
Do not use
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.

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, 5.5, 5.7, 5.9)]* .

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

- Bupivacaine Hydrochloride Injection is not for intrathecal use.
- Discard unused portions of solution not containing preservatives, i.e., those supplied in single-dose vials, following initial use.
- Visually inspect this product for particulate matter and discoloration prior to administration whenever solution and container permit. Bupivacaine Hydrochloride Injection 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 is not recommended because of insufficient data on the clinical use of such mixtures.

Administration Precautions

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

(adequacy of oxygenation and ventilation) vital signs and the patient's level of consciousness after each local anesthetic injection.

2.2 Recommended Concentrations and Dosages of Bupivacaine Hydrochloride Injection

The dosage of Bupivacaine Hydrochloride Injection administered varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. Administer the smallest dosage and concentration required to produce the desired result.

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

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

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

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

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

At recommended dosages, Bupivacaine Hydrochloride 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. Types of Block and Recommended Bupivacaine Hydrochloride Injection Concentrations

Bupivacaine Hydrochloride Injection Concentration	**Motor Function**
0.25% (2.5 mg/mL)	When used for caudal, epidural, or peripheral nerve block, produces incomplete motor block. Should be used for operations in which muscle relaxation is not important, or when another means of providing muscle relaxation is used concurrently. Onset of action may be slower than with the 0.5% (5 mg/mL) or 0.75% (7.5 mg/mL) solutions.
0.5% (5 mg/mL)	Provides motor blockade for caudal, epidural, or nerve block, but muscle relaxation may be inadequate for operations in which complete muscle relaxation is essential.
0.75% (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.

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

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

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

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

Type of Block	**Concentration of Bupivacaine Hydrochloride Injection**	**Each Dose**		**Motor Block***
		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)	
	0.5% (5 mg/mL)	5–35	25–175	moderate to

Peripheral nerve block	†	(without epinephrine)	(without epinephrine)	complete
		5–45 (with epinephrine)	25–225 (with epinephrine)	
	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

* With continuous (intermittent) techniques, repeat doses increase the degree of motor block. The first repeat dose of 0.5% (5 mg/mL) may produce complete motor block. Intercostal nerve block with 0.25% (2.5 mg/mL) also may produce complete motor block for intra-thoracic and upper intra-abdominal surgery.
† Solutions with or without epinephrine (i.e., applies to Bupivacaine Hydrochloride Injection.
‡ For single-dose use; not for intermittent epidural technique. Not for obstetrical anesthesia.

2.3 Use in Epidural Anesthesia

During epidural administration, administer Bupivacaine Hydrochloride Injection, 0.5% (5 mg/mL) and 0.75% (7.5 mg/mL) solutions in incremental doses of 3 mL to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Administer injections slowly, with frequent aspirations before and during the injection to avoid intravascular injection. Perform syringe aspirations before and during each supplemental injection in continuous (intermittent) catheter techniques. In obstetrics, use ONLY the 0.5% (5 mg/mL) and 0.25% (2.5 mg/mL) concentrations of Bupivacaine Hydrochloride Injection *[see Warnings and Precautions (5.1)];* incremental doses of 3 mL to 5 mL of the 0.5% (5 mg/mL) solution not exceeding 50 mg to 100 mg at any dosing interval are recommended. Repeat doses should be preceded by a test dose containing epinephrine if not clinically contraindicated. Use only the single-dose vials for caudal or epidural anesthesia; avoid use of the multiple-dose vials for these procedures, which contain a preservative *[see*

Dosage and Administration (2.1), Warnings and Precautions (5.9)] .

2.6 Use in Ophthalmic Surgery

When Bupivacaine Hydrochloride Injection 0.75% (7.5 mg/mL) is used for retrobulbar block, complete corneal anesthesia usually precedes onset of clinically acceptable external ocular muscle akinesia. Therefore, presence of akinesia rather than anesthesia alone should determine readiness of the patient for surgery *[see Warnings and Precautions (5.15)]* .

3 DOSAGE FORMS AND STRENGTHS

Bupivacaine Hydrochloride Injection, USP is a clear, colorless solution available as:

- 0.5% (50 mg/10 mL) (5 mg/mL) in single-dose teartop vials.

4 CONTRAINDICATIONS

Bupivacaine Hydrochloride Injection is contraindicated in:

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

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Cardiac Arrest with Use of Bupivacaine Hydrochloride Injection in Obstetrical Anesthesia

There have been reports of cardiac arrest with difficult resuscitation or death during use of Bupivacaine Hydrochloride Injection for epidural anesthesia in obstetrical patients. In most cases, this has followed use of the 0.75% (7.5 mg/mL) concentration. Resuscitation has been difficult or impossible despite apparently adequate preparation and appropriate management. Cardiac arrest has occurred after convulsions resulting from systemic toxicity, presumably following unintentional intravascular injection. The 0.75% (7.5 mg/mL) concentration of Bupivacaine Hydrochloride Injection is not recommended for obstetrical anesthesia and should be reserved for surgical procedures where a high degree of muscle relaxation and prolonged effect are necessary.

5.2 Dose-Related Toxicity

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

Possible early warning signs of central nervous system (CNS) toxicity are restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and

lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, CNS depression, or drowsiness. Delay in proper management of dose-related toxicity, underventilation from any cause, and/or altered sensitivity may lead to the development of acidosis, cardiac arrest, and, possibly, death.

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

Injection of repeated doses of Bupivacaine Hydrochloride Injection may cause significant increases in plasma levels with each repeated dose due to slow accumulation of the drug or its metabolites, or to slow metabolic degradation. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with their age and physical status.

5.3 Methemoglobinemia

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

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

5.5 Chondrolysis with Intra-Articular Infusion

Intra-articular infusions of local anesthetics including Bupivacaine Hydrochloride Injection following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of gleno-humeral chondrolysis have been described in pediatric and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are associated with chondrolysis. The time of onset of symptoms, such as joint pain, stiffness and loss of motion can be variable, but may begin as early as the 2 ndmonth after surgery. Currently, there is no effective treatment for chondrolysis; patients who experienced chondrolysis have required additional diagnostic and

therapeutic procedures and some required arthroplasty or shoulder replacement.

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

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

5.9 Risk of Systemic Toxicities with Unintended Intravascular or Intrathecal Injection

Unintended intravascular or intrathecal injection of Bupivacaine Hydrochloride Injection may be associated with systemic toxicities, including CNS or cardiorespiratory depression and coma, progressing ultimately to respiratory arrest. Unintentional intrathecal injection during the intended performance of caudal or lumbar epidural block or nerve blocks near the vertebral column has resulted in underventilation or apnea ("Total or High Spinal"). A high spinal has been characterized by paralysis of the legs, loss of consciousness, respiratory paralysis, and bradycardia *[see Adverse Reactions (6)]* .

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

5.10 Risk of Toxicity in Patients with Hepatic Impairment

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

5.11 Risk of Use in Patients with Impaired Cardiovascular Function

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

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

Small doses of local anesthetics (e.g., Bupivacaine Hydrochloride Injection) injected into the head and neck area, including retrobulbar, dental, and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care. Confusion, convulsions, respiratory depression, and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral

circulation. They may also be due to puncture of the dural sheath of the optic nerve during retrobulbar block with diffusion of any local anesthetic along the subdural space to the midbrain. Monitor circulation and respiration and constantly observe patients receiving Bupivacaine Hydrochloride Injection blocks. Resuscitative equipment and drugs, and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded *[see Dosage and Administration (2.2)].*

5.15 Risk of Respiratory Arrest with Use in Ophthalmic Surgery

Clinicians who perform retrobulbar blocks should be aware that there have been reports of respiratory arrest following local anesthetic injection. Prior to retrobulbar block (e.g., with Bupivacaine Hydrochloride Injection), as with all other regional procedures, resuscitative equipment and drugs, and personnel to manage respiratory arrest or depression, convulsions, and cardiac stimulation or depression should be immediately available *[see Warnings and Precautions (5.14)].* As with other anesthetic procedures, patients should be constantly monitored following ophthalmic blocks for signs of these adverse reactions, which may occur following relatively low total doses.

A concentration of 0.75% bupivacaine is indicated for retrobulbar block; however, this concentration is not indicated for any other peripheral nerve block, including the facial nerve, and not indicated for local infiltration, including the conjunctiva *[see Indications and Usage (1)].*

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

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

6 ADVERSE REACTIONS

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

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

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

Adverse reactions to Bupivacaine Hydrochloride Injection are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to 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 cannot be avoided, monitor patients for neurologic and cardiovascular effects related to local anesthetic systemic toxicity *[see Dosage and Administration (2.1), Warnings and Precautions (5.2)]* .

7.5 Drugs Associated with Methemoglobinemia

Patients who are administered Bupivacaine Hydrochloride Injection are at increased risk of developing methemoglobinemia when concurrently exposed to the 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, ifosfamide, rasburicase
Antibiotics	dapsone, nitrofurantoin, para-aminosalicylic acid, sulfonamides
Antimalarials	chloroquine, primaquine
Anticonvulsants	phenobarbital, phenytoin, sodium valproate
Other drugs	acetaminophen, metoclopramide, quinine, sulfasalazine

7.6 Potent Inhalation Anesthetics

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

administration of potent inhalation anesthetics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

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

Local anesthetics rapidly cross the placenta, and when used for epidural, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, fetal, and neonatal toxicity *[see Clinical Pharmacology (12.3)].* The incidence and degree of toxicity depend upon the procedure performed, the type, and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the CNS, peripheral vascular tone, and cardiac function.

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

Clinical Considerations

Maternal Adverse Reactions

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. The supine position is dangerous in pregnant women at term because of aortocaval compression by the gravid uterus. Therefore, during treatment of systemic toxicity, maternal hypotension or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels be accomplished. Elevating the patient's legs will also help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously and electronic fetal monitoring is highly advisable.

Labor or Delivery

Epidural, caudal, or pudendal anesthesia may alter the forces of parturition through

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

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

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

Data

Animal Data

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

Bupivacaine hydrochloride was administered subcutaneously to rats at doses of 4.4, 13.3, & 40 mg/kg and to rabbits at doses of 1.3, 5.8, & 22.2 mg/kg during the period of organogenesis (implantation to closure of the hard palate). The high doses are comparable to the daily MRHD of 400 mg/day on a mg/m ^{2}BSA basis. No embryo-fetal effects were observed in rats at the high dose which caused increased maternal lethality. An increase in embryo-fetal deaths was observed in rabbits at the high dose in the absence of maternal toxicity with the fetal No Observed Adverse Effect Level representing approximately 0.3 times the MRHD on a BSA basis.

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

8.2 Lactation

Risk Summary

Lactation studies have not been conducted with bupivacaine. Bupivacaine has been reported to be excreted in human milk suggesting that the nursing infant could be theoretically exposed to a dose of the drug. Bupivacaine Hydrochloride Injection should be administered to lactating women only if clearly indicated. Studies assessing the effects of Bupivacaine Hydrochloride Injection in breastfed children have not been performed. Studies to assess the effect of Bupivacaine Hydrochloride Injection on milk production or excretion have not been performed. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bupivacaine and any potential adverse effects on the breastfed child from bupivacaine or from the underlying maternal condition.

8.4 Pediatric Use

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

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

8.5 Geriatric Use

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

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

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

This product is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Elderly patients may require lower doses of Bupivacaine Hydrochloride Injection.

8.6 Hepatic Impairment

Amide-type local anesthetics, such as bupivacaine, are metabolized by the liver. Patients with severe hepatic impairment, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations, and potentially local anesthetic systemic toxicity. Therefore, consider reduced dosing and increased monitoring for local anesthetic systemic toxicity in patients with moderate to severe hepatic impairment treated with Bupivacaine Hydrochloride Injection, especially with repeat doses *[see Warnings and Precautions (5.10)]* .

8.7 Renal Impairment

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

10 OVERDOSAGE

Clinical Presentation

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

If not treated immediately, convulsions with simultaneous hypoxia, hypercarbia, and acidosis plus myocardial depression from the direct effects of bupivacaine may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities, including apnea, may occur. Hypoventilation or apnea due to unintentional intrathecal injection of Bupivacaine Hydrochloride Injection may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If

cardiac arrest should occur, successful outcome may require prolonged resuscitative efforts.

Management

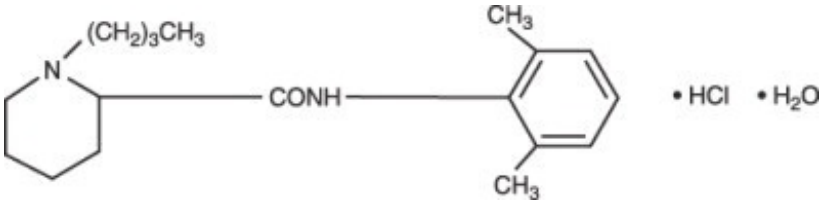
The first step in the management of systemic toxic reactions, as well as hypoventilation or apnea due to unintentional intrathecal injection of Bupivacaine Hydrochloride Injection, consists of immediateattention to the establishment and maintenance of a patent airway and effective assisted or controlled 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 Advanced 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 is by injection, for infiltration, perineural, caudal, epidural, or retrobulbar use. *[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 5 mg of bupivacaine hydrochloride (equivalent to 4.44 mg of bupivacaine, respectively), sodium chloride for isotonicity, sodium hydroxide or hydrochloric acid to adjust the pH between 4 and 6.5, in water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bupivacaine blocks the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as

follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

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 a period of analgesia that persists after the resolution of the block and return of sensation.

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

12.3 Pharmacokinetics

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

Absorption

The rate of systemic absorption of bupivacaine is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution. A dilute concentration of epinephrine (1:200,000) usually reduces the rate of absorption and peak plasma concentration of bupivacaine, permitting the use of moderately larger total doses and sometimes prolonging the duration of action *[see Dosage and Administration (2)]* .

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

Distribution

Bupivacaine appears to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/maternal ratios of bupivacaine appear to be inversely related to the degree of plasma protein binding, because only the

free, unbound drug is available for placental transfer. Bupivacaine with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, nonionized drugs readily enter the fetal blood from the maternal circulation.

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

Pharmacokinetic studies on the plasma profile of bupivacaine after direct intravenous injection (Bupivacaine Hydrochloride Injection is not approved for intravenous use) suggest a three-compartment open model. The first compartment is represented by the rapid intravascular distribution of the drug. The second compartment represents the equilibration of the drug throughout the highly perfused organs such as the brain, myocardium, lungs, kidneys, and liver. The third compartment represents an equilibration of the drug with poorly perfused tissues, such as muscle and fat.

Elimination

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

Metabolism

Amide-type local anesthetics such as bupivacaine are metabolized primarily in the liver via conjugation with glucuronic acid. Pipecoloxylidine is the major metabolite of bupivacaine. The elimination of drug from tissue distribution depends largely upon the availability of binding sites in the circulation to carry it to the liver where it is metabolized.

Excretion

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

Specific Populations

Geriatric Patients

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

Patients with Hepatic Impairment

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

Patients with Renal Impairment

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

The mutagenic potential of bupivacaine hydrochloride has not been determined.

Impairment of Fertility

The effect of bupivacaine on fertility has not been determined.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

Unit of Sale	**Concentration**
NDC 0409-1162-01 Tray of 25 single-dose teartop vials	0.5% **50 mg/10 mL** (5 mg/mL)
NDC 0409-1162-02 Tray of 25 single-dose teartop vials	0.5% **150 mg/30 mL** (5 mg/mL)

For single-dose vials: Discard unused portion.

17 PATIENT COUNSELING INFORMATION

Allergic-Type Reactions

Assess if the patient has had allergic-type reactions to amide-type local anesthetics *[see Contraindications (4), Adverse Reactions (6)].*

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

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

Instructions After Dental Injection of Bupivacaine Hydrochloride Injection

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

Methemoglobinemia

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

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

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

LAB-1176-6.0

Methylprednisolone Acetate Injectable Suspension, USP

NOT FOR USE IN NEONATES
CONTAINS BENZYL ALCOHOL
(NOT for Intravenous Use)

SAGENT®
Rx only

DESCRIPTION

Methylprednisolone Acetate Injectable Suspension, USP is an anti-inflammatory glucocorticoid for intramuscular, intra-articular, soft tissue, or intralesional injection. It is available in 40 mg per mL.

Each mL of these preparations contains:

Methylprednisolone acetate.....40 mg

Polyethylene glycol 3350.....29.1 mg

Polysorbate 80.....1.94 mg

Monobasic sodium phosphate.....6.8 mg

Dibasic sodium phosphate, USP.....1.42 mg

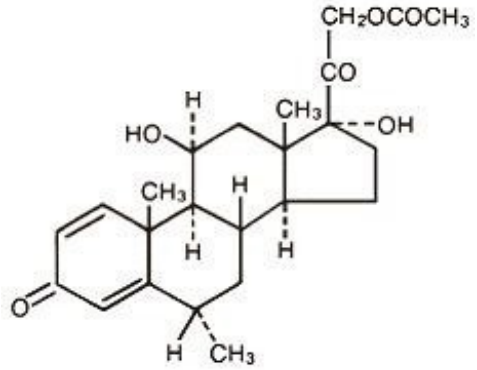
Benzyl alcohol added as a preservative.....9.16 mg

Sodium Chloride was added to adjust tonicity.

When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid.

The pH of the finished product remains within the USP specified range (e.g., 3.5 to 7.0).

The chemical name for methylprednisolone acetate is pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-,(6α,11ß)- and the molecular weight is 416.51. The structural formula is represented below:



Methylprednisolone Acetate Injectable Suspension, USP, sterile aqueous suspension, contains methylprednisolone acetate which is the 6-methyl derivative of prednisolone. Methylprednisolone acetate is a white or practically white, odorless, crystalline powder which melts at about 215° with some decomposition. It is soluble in dioxane, sparingly soluble in acetone, alcohol, chloroform, and methanol, and slightly soluble in ether. It is practically insoluble in water.

CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids.

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

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

INDICATIONS AND USAGE

A. For Intramuscular Administration

When oral therapy is not feasible and the strength, dosage form, and route of administration of the drug reasonably lend the preparation to the treatment of the condition, the intramuscular use of Methylprednisolone Acetate Injectable Suspension, sterile aqueous suspension, is indicated as follows:

*Allergic States:*Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, 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 (systemic therapy) and ulcerative colitis.

*Hematologic Disorders:*Acquired (autoimmune) hemolytic anemia, congenital (erythroid) hypoplastic anemia (Diamond Blackfan anemia), pure red cell aplasia, select cases of secondary thrombocytopenia.

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

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

*Nervous System:*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.

B. For Intra-articular or Soft Tissue Administration

(See WARNINGS)

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

C. For Intralesional Administration

Methylprednisolone Acetate Injectable Suspension is indicated for intralesional use in alopecia areata, discoid lupus erythematosus, keloids, localized hypertrophic, infiltrated, inflammatory lesions of granuloma annulare, lichen planus, lichen simplex chronicus (neurodermatitis), and psoriatic plaques, necrobiosis lipoidica diabeticorum.

Methylprednisolone Acetate Injectable Suspension also may be useful in cystic tumors of an aponeurosis or tendon (ganglia).

CONTRAINDICATIONS

Methylprednisolone acetate is contraindicated in patients with known hypersensitivity to the product and its constituents.

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

Methylprednisolone acetate sterile aqueous suspension is contraindicated for intrathecal administration. Reports of severe medical events have been associated with this route of administration.

Methylprednisolone acetate is contraindicated for use in premature infants because the formulation contains benzyl alcohol. (See **WARNINGS**and **PRECAUTIONS: Pediatric Use**.)

Methylprednisolone acetate is contraindicated in systemic fungal infections, except when administered as an intra-articular injection for localized joint conditions (see **WARNINGS: Infections, Fungal Infections**).

WARNINGS

Serious Neurologic Adverse Reactions with Epidural Administration

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

General

This product contains benzyl alcohol, which is potentially toxic when administered locally to neural tissue. 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 in 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**).

Multidose use of methylprednisolone acetate sterile aqueous suspension from a single vial requires special care to avoid contamination. Although initially sterile, any multidose use of vials may lead to contamination unless strict aseptic technique is observed. Particular care, such as use of disposable sterile syringes and needles, is necessary.

Injection of methylprednisolone acetate may result in dermal and/or subdermal changes, forming depressions in the skin at the injection site.

In order to minimize the incidence of dermal and subdermal atrophy, care must be exercised not to exceed recommended doses in injections. Multiple

small injections into the area of the lesion should be made whenever possible. The technique of intra-articular and intramuscular injection should include precautions against injection or leakage into the dermis. Injection into the deltoid muscle should be avoided because of a high incidence of subcutaneous atrophy.

It is critical that, during administration of methylprednisolone acetate, appropriate technique be used and care taken to ensure proper placement of drug.

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy.

Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, or after the stressful situation (see **ADVERSE REACTIONS**).

Results from one multicenter, randomized, placebo-controlled study with methylprednisolone hemisuccinate, an IV 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 methylprednisolone acetate, 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 used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Literature reports suggest an apparent association between the 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

Hypothalamic-pituitary adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia: Monitor patients for these conditions with chronic use.

Corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. 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.

Infections

General

Persons 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. Infections 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, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may mask some signs of current infection. Do not use intra-articularly, intrabursally, or for intratendinous administration for local effect in the presence of acute local 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 **CONTRAINDICATIONS**and **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,*and *Toxoplasma.*

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

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

Corticosteroids should not be used in cerebral malaria. There is currently no evidence of benefit from steroids in this condition.

Tuberculosis

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

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

Vaccinations

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.

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 systemic corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should be used cautiously in patients with ocular herpes simplex because of corneal perforation. Corticosteroids should not be used in active ocular herpes simplex.

PRECAUTIONS

General

When multidose vials are used, special care to prevent contamination of the contents is essential. A povidone-iodine solution or similar product is recommended to cleanse the vial top prior to aspiration of contents. (See **WARNINGS**.)

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

Caution is required in patients with systemic sclerosis because an increased incidence of scleroderma renal crisis has been observed with corticosteroids, including methylprednisolone.

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.

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.

Gastrointestinal

Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and non-specific 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 due to decreased metabolism of corticosteroids in patients with cirrhosis.

Parenteral Administration

Intra-articular injected corticosteroids may be systemically absorbed.

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

A marked increase in pain associated 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.

Musculoskeletal

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (e.g., 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

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 creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

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

Ophthalmic

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

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

Information for the Patient

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 (e.g., 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 (see **PRECAUTIONS: Drug Interactions, Hepatic Enzyme Inhibitors**).

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

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

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

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

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

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

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

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

*Hepatic Enzyme Inducers (e.g., barbiturates, phenytoin, carbamazepine, rifampin):*Drugs which induce cytochrome P450 3A4 enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

*Hepatic Enzyme Inhibitors (e.g., ketoconazole, macrolide antibiotics such as erythromycin and troleandomycin):*Drugs which inhibit cytochrome P450 3A4 have the potential to result in increased plasma concentrations of corticosteroids.

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

*Nonsteroidal anti-inflammatory drugs (NSAIDs):*Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with concurrent use of 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 attenuated 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, Vaccinations**).

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.

Corticosteroids have been shown to impair fertility in male rats.

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.

This product contains benzyl alcohol as a preservative.

Benzyl alcohol can cross the placenta. See **PRECAUTIONS: Pediatric Use**.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to continue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

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 ordinarily delivers 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. The risk of benzyl alcohol toxicity depends on the quantity administered and the hepatic capacity to detoxify the chemical. 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 nephritic syndrome (patients >2 years of age) and aggressive lymphomas and leukemias (patients >1 month of age). Other indications for pediatric use of corticosteroids (e.g., severe asthma and wheezing) are based on adequate and well-controlled clinical 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

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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.

ADVERSE REACTIONS

The following adverse reactions have been reported with methylprednisolone acetate or other corticosteroids:

Allergic reactions:Allergic or hypersensitivity reactions, anaphylactoid reaction, anaphylaxis, angioedema.

Blood and lymphatic system disorders:Leukocytosis.

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

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

Endocrine:Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, 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), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible subsequent perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic:Negative nitrogen balance due to protein catabolism.

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

Neurologic/Psychiatric:Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo.

Ophthalmic:Exophthalmoses, glaucoma, increased intraocular pressure, posterior subcapsular cataracts.

Other:Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, injection site infections following non-sterile administration (see **WARNINGS**), malaise, moon face, weight gain.

The following adverse reactions have been reported with the following routes of administration:

Intrathecal/Epidural:Arachnoiditis, bowel/bladder dysfunction, headache, meningitis, paraparesis/paraplegia, seizures, sensory disturbances.

Intranasal:Allergic reactions, rhinitis, temporary/permanent visual impairment including blindness.

Ophthalmic:Increased intraocular pressure, infection, ocular and periocular inflammation including allergic reactions, residue or slough at injection site, temporary/permanent visual impairment including blindness.

Miscellaneous injection sites*(scalp, tonsillar fauces, sphenopalatine ganglion)**:***Blindness.

To report SUSPECTED ADVERSE REACTIONS, contact Sagent Pharmaceuticals, Inc. at 1-866-625-1618 or FDA at 1-800-FDA-1088 or 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

NOTE: CONTAINS BENZYL ALCOHOL (see **WARNINGS**and **PRECAUTIONS: Pediatric Use)**

Because of possible physical incompatibilities, methylprednisolone acetate sterile aqueous suspension should not be diluted or mixed with other solutions.

The initial dosage of parenterally administered methylprednisolone acetate will vary from 4 to 120 mg, depending on the specific disease entity being treated. 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.

A. Administration for Local Effect

Therapy with methylprednisolone acetate does not obviate the need for the conventional measures usually employed. Although this method of treatment will ameliorate symptoms, it is in no sense a cure and the hormone has no effect on the cause of the inflammation.

1. Rheumatoid Arthritis and Osteoarthritis. The dose for intra-articular administration depends upon the size of the joint and varies with the severity of the condition in the individual patient. In chronic cases, injections may be repeated at intervals ranging from one to five or more weeks, depending upon the degree of relief obtained from the initial injection. The doses in the following table are given as a general guide:

Size of Joint	*Examples*	*Range of Dosage*
Large	Knees Ankles Shoulders	20 to 80 mg
Medium	Elbows Wrists	10 to 40 mg
Small	Metacarpophalangeal Interphalangeal Sternoclavicular Acromioclavicular	4 to 10 mg

Procedure: It is recommended that the anatomy of the joint involved be reviewed

before attempting intra-articular injection. In order to obtain the full anti-inflammatory effect, it is important that the injection be made into the synovial space. Employing the same sterile technique as for a lumbar puncture, a sterile 20 to 24 gauge needle (on a dry syringe) is quickly inserted into the synovial cavity. Procaine infiltration is elective. The aspiration of only a few drops of joint fluid proves the joint space has been entered by the needle. *The injection site for each joint is determined by that location where the synovial cavity is most superficial and most free of large vessels and nerves.*With the needle in place, the aspirating syringe is removed and replaced by a second syringe containing the desired amount of methylprednisolone acetate. The plunger is then pulled outward slightly to aspirate synovial fluid and to make sure the needle is still in the synovial space. After injection, the joint is moved gently a few times to aid mixing of the synovial fluid and the suspension. The site is covered with a small sterile dressing.

Suitable sites for intra-articular injection are the knee, ankle, wrist, elbow, shoulder, phalangeal, and hip joints. Since difficulty is not infrequently encountered in entering the hip joint, precautions should be taken to avoid any large blood vessels in the area. Joints not suitable for injection are those that are anatomically inaccessible such as the spinal joints and those like the sacroiliac joints that are devoid of synovial space. Treatment failures are most frequently the result of failure to enter the joint space. Little or no benefit follows injection into surrounding tissue. If failures occur when injections into the synovial spaces are certain, as determined by aspiration of fluid, repeated injections are usually futile.

If a local anesthetic is used prior to injection of methylprednisolone acetate, the anesthetic package insert should be read carefully and all the precautions observed.

2. Bursitis. The area around the injection site is prepared in a sterile way and a wheal at the site made with 1 percent procaine hydrochloride solution. A 20 to 24 gauge needle attached to a dry syringe is inserted into the bursa and the fluid aspirated. The needle is left in place and the aspirating syringe changed for a small syringe containing the desired dose. After injection, the needle is withdrawn and a small dressing applied.

3. Miscellaneous: Ganglion, Tendinitis, Epicondylitis. In the treatment of conditions such as tendinitis or tenosynovitis, care should be taken following application of a suitable antiseptic to the overlying skin to inject the suspension into the tendon sheath rather than into the substance of the tendon. The tendon may be readily palpated when placed on a stretch. When treating conditions such as epicondylitis, the area of greatest tenderness should be outlined carefully and the suspension infiltrated into the area. For ganglia of the tendon sheaths, the suspension is injected directly into the cyst. In many cases, a single injection causes a marked decrease in the size of the cystic tumor and may effect disappearance. The usual sterile precautions should be observed, of course, with each injection.

The dose in the treatment of the various conditions of the tendinous or bursal structures listed above varies with the condition being treated and ranges from 4 to 30 mg. In recurrent or chronic conditions, repeated injections may be necessary.

4. Injections for Local Effect in Dermatologic Conditions. Following cleansing with an appropriate antiseptic such as 70% alcohol, 20 to 60 mg is injected into the lesion. It may be necessary to distribute doses ranging from 20 to 40 mg by repeated local injections in the case of large lesions. Care should be taken to avoid injection of sufficient material to cause blanching since this may be followed by a small slough. One to four injections are usually employed, the intervals between injections varying with the type of

lesion being treated and the duration of improvement produced by the initial injection.

When multidose vials are used, special care to prevent contamination of the contents is essential. (See WARNINGS.)

B. Administration for Systemic Effect

The intramuscular dosage will vary with the condition being treated. When employed as a temporary substitute for oral therapy, a single injection during each 24-hour period of a dose of the suspension equal to the total daily oral dose of methylprednisolone tablets, USP is usually sufficient. When a prolonged effect is desired, the weekly dose may be calculated by multiplying the daily oral dose by 7 and given as a single intramuscular injection.

In pediatric patients, the initial dose of methylprednisolone acetate may vary depending upon the specific disease entity being treated. The range of initial doses is 0.11 to 1.6 mg/kg/day. Dosage must be individualized according to the severity of the disease and response of the patient.

In patients with the **adrenogenital syndrome**, a single intramuscular injection of 40 mg every two weeks may be adequate. For maintenance of patients with **rheumatoid arthritis**, the weekly intramuscular dose will vary from 40 to 120 mg. The usual dosage for patients with **dermatologic lesions**benefited by systemic corticoid therapy is 40 to 120 mg of methylprednisolone acetate administered intramuscularly at weekly intervals for one to four weeks. In acute severe dermatitis due to poison ivy, relief may result within 8 to 12 hours following intramuscular administration of a single dose of 80 to 120 mg. In chronic contact dermatitis, repeated injections at 5 to 10 day intervals may be necessary. In seborrheic dermatitis, a weekly dose of 80 mg may be adequate to control the condition.

Following intramuscular administration of 80 to 120 mg to asthmatic patients, relief may result within 6 to 48 hours and persist for several days to two weeks.

If signs of stress are associated with the condition being treated, the dosage of the suspension should be increased. If a rapid hormonal effect of maximum intensity is required, the intravenous administration of highly soluble methylprednisolone sodium succinate is indicated.

For the purpose of comparison, the following is the equivalent milligram dose 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.

HOW SUPPLIED

Methylprednisolone Acetate Injectable Suspension, USP, sterile aqueous suspension, is supplied as follows:

NDC	Methylprednisolone Acetate Injectable Suspension, USP (40 mg per mL)	Package Factor
25021-820-05	200 mg per 5 mL Multi-Dose Vial	1 vial per carton
25021-820-10	400 mg per 10 mL Multi-Dose Vial	1 vial per carton

Storage Conditions

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

Sterile, Nonpyrogenic.

The container closure is not made with natural rubber latex.

SAGENT®

Mfd. for SAGENT Pharmaceuticals
Schaumburg, IL 60195 (USA)
Made in India

June 2021

SAGENT Pharmaceuticals®

Povidone-Iodine Prep Pad

Active ingredient

Povidone-Iodine, 10% w/w

Purpose

Antiseptic

Uses

- First aid antiseptic to help prevent infection in minor cuts, scrapes and burns

Warnings

For external use only.

Do not use

- in the eyes

- longer than 1 week unless directed by a physician
- on individuals who are allergic or sensitive to iodine
- or apply over large areas of the body

Stop use and ask a doctor if
- irritation and redness develop
- condition persists for more than 72 hours
- in case of deep or puncture wounds, animal bites or serious burns

Keep out of reach of children.

If swallowed, get medical assistance or immediately contact a Poison Control Center.

Directions
- clean the affected area
- apply a small amount of this product on the area 1 to 3 times daily.
- may be covered with a sterile bandage
- if bandaged, let dry first

Other information
- do not flush
- protect from freezing, avoid excessive heat

Inactive ingredients

citric acid, disodium phosphate, water

PRINCIPAL DISPLAY PANEL

NDC: 76420-520-01

Rx Only

Physicians EZ Use
M-pred Injection Kit™

Kit Contains

1 Bupivacaine HCl 0.5% Single Dose Vial (10mL)

1 Methylprednisolone Acetate Injectable Suspension, USP 40mg/mL (5mL)

1 Povidone-Iodine Prep Pad

1 Pair Nitrile Powder Free Sterile Gloves (M)

1 Drape

1 Adhesive Bandage

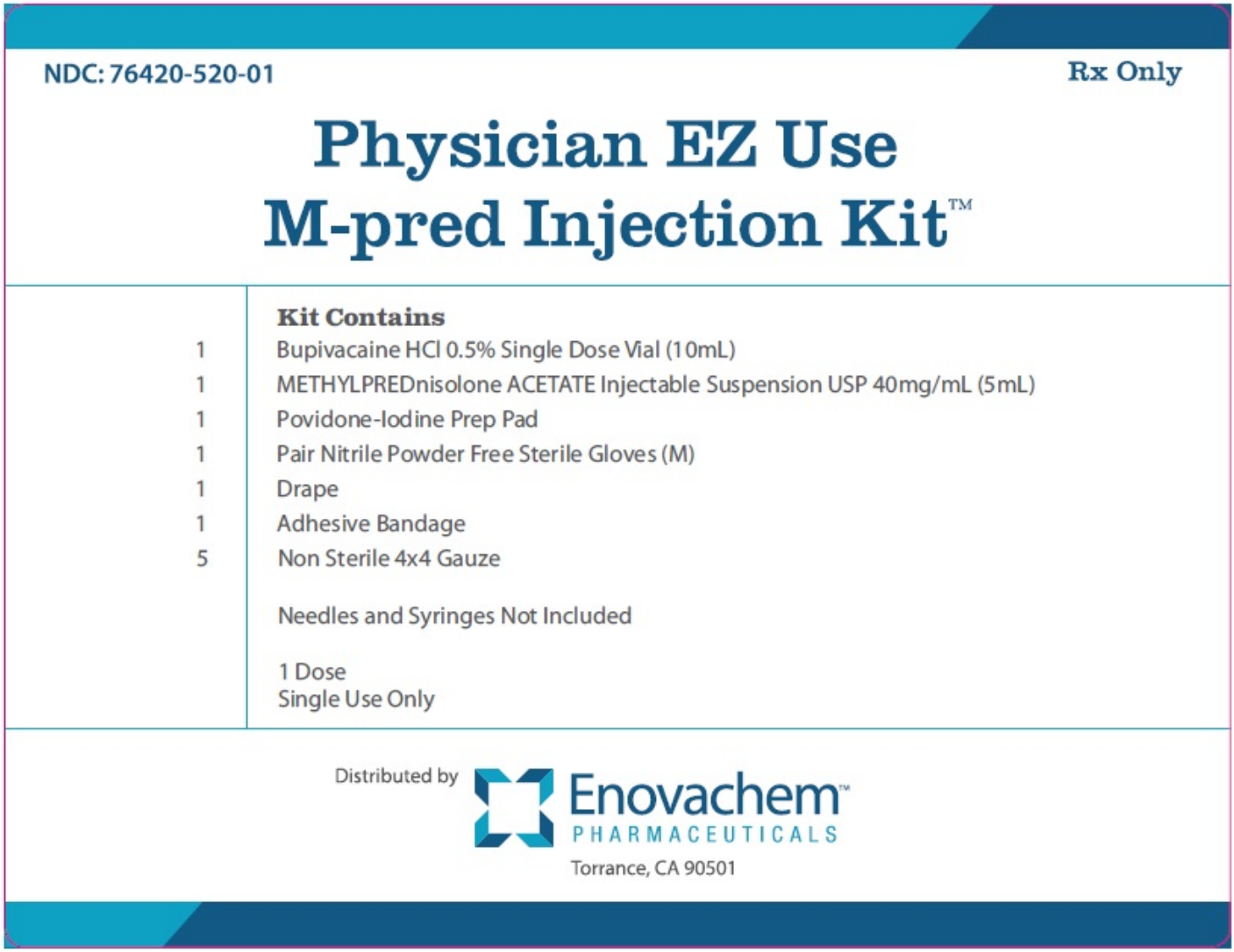
5 Non Sterile 4x4 Gauze

Needles and Syringes Not Included

1 Dose

Single Use Only

Distributed by
Enovachem™
PHARMACEUTICALS
Torrance, CA 90501



PHYSICIANS EZ USE M-PRED

methylprednisolone acetate, bupivacaine hydrochloride, povidone-iodine kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:76420-520

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**

1	NDC:76420-520-01	1 in 1 CARTON; Type 1: Convenience Kit of Co-Package	05/30/2013	

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1 VIAL	5 mL
Part 2	1 VIAL, SINGLE-DOSE	10 mL
Part 3	1 PACKET	1 mL

Part 1 of 3

METHYLPREDNISOLONE ACETATE

methylprednisolone acetate injection, suspension

Product Information	
Item Code (Source)	NDC:25021-820
Route of Administration	INTRA-ARTICULAR, INTRAMUSCULAR, INTRASYNOVIAL, INTRALESIONAL, SOFT TISSUE

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
METHYLPREDNISOLONE ACETATE (UNII: 43502P7F0P) (METHYLPREDNISOLONE - UNII:X4W7ZR7023)	METHYLPREDNISOLONE ACETATE	40 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
POLYETHYLENE GLYCOL 3350 (UNII: G2M7P15E5P)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
SODIUM PHOSPHATE, MONOBASIC, UNSPECIFIED FORM (UNII: 3980JIH2SW)	
SODIUM PHOSPHATE, DIBASIC (UNII: GR686LBA74)	
BENZYL ALCOHOL (UNII: LKG8494WBH)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:25021-820-05	1 in 1 CARTON		
1		5 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	ANDA201835	11/15/2021	

Part 2 of 3

BUPIVACAINE HYDROCHLORIDE

bupivacaine hydrochloride injection, solution

Product Information

Item Code (Source)	NDC:0409-1162
Route of Administration	EPIDURAL, INTRACAUDAL, PERINEURAL

Active Ingredient/Active Moiety

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

Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	8.1 mg in 1 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
WATER (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 3 of 3

POVIDONE-IODINE PREP PADS MEDIUM

povidone-iodine cloth

Product Information	
Item Code (Source)	NDC:53329-941
Route of Administration	TOPICAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
POVIDONE-IODINE (UNII: 85H0HZU99M) (IODINE - UNII:9679TC07X4)	IODINE	10 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS (UNII: 22ADO53M6F)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
WATER (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:53329-941-30	100 in 1 BOX		
1		1 mL in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
OTC monograph not final	part333E	01/01/2007	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		05/30/2013	

Labeler - Asclemed USA, Inc. (059888437)

Establishment

Name	Address	ID/FEI	Business Operations
ASCLEMED USA INC. DBA ENOVACHEM		059888437	manufacture(76420-520)

Revised: 7/2023

Asclemed USA, Inc.