HIGHLIGHTS OF PRESCRIBING INFORMATION

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

CARBOCAINE® (mepivacaine hydrochloride) injection, for local infiltration, peripheral, caudal, or epidural block
Initial U.S. Approval: 1960

---------- INDICATIONS AND USAGE----------

CARBOCAINE contains mepivacaine, an amide local anesthetic. CARBOCAINE is indicated in adults and pediatric patients for the production of local or regional analgesia and/or anesthesia by administration of local infiltration, peripheral nerve block techniques, and central neural techniques including epidural and caudal blocks. 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
CARBOCAINE is not intended for spinal anesthesia or dental use. (1)

----------DOSAGE AND ADMINISTRATION----------

- Not for intrathecal use. (2.1)
- Carbocaine is supplied both with (multiple-dose vials) and without (single-dose-vials) antimicrobial preservatives. (2.1)
- Avoid use of solutions containing antimicrobial preservatives (i.e., multiple-dose vials) for epidural or caudal anesthesia. (2.1, 5.3)
- CARBOCAINE without antimicrobial preservative is recommended for use as a test dose with epinephrine prior to caudal and lumbar epidural blocks when clinical conditions permit. (2.4)
- See full prescribing information for:
  - Adults: Recommended concentrations and dosages of CARBOCAINE according to type of block. (2.2)
  - Pediatric patients: Recommended concentrations and dosages of CARBOCAINE according to age group and weight. (2.2)
  - Additional dosage and administration information pertaining to use in epidural anesthesia and test dose for caudal and lumbar epidural blocks. (2.3, 2.4)

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

Injection:

- 1% (300 mg/30 mL) (10 mg/mL) single-dose vials. (3)
- 1% (500 mg/50 mL) (10 mg/mL) multiple-dose vials. (3)
- 1.5% (450 mg/30 mL) (15 mg/mL) single-dose vials. (3)
- 2% (400 mg/20 mL) (20 mg/mL) single-dose vials. (3)
- 2% (1,000 mg/50 mL) (20 mg/mL) multiple-dose vials. (3)

---------- CONTRAINDICATIONS ----------

Known hypersensitivity to mepivacaine or to any local anesthetic agent of the amide-type or to other components of CARBOCAINE. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Dose-Related Toxicity: Monitor cardiovascular and respiratory vital signs and patient's state of consciousness after injection of CARBOCAINE. (5.1)
- Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use. See full prescribing information for more detail on managing these risks. (5.2)
- Chondrolysis with Intra-Articular Infusion: Intra-articular infusions of local anesthetics including CARBOCAINE following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of chondrolysis in patients receiving such infusions. (5.4)
- Risk of Systemic Toxicities with Unintended Intravascular or Intrathecal Injection: Unintended intravascular or intrathecal injection may be associated with systemic toxicities, including CNS or cardiorespiratory depression and coma, progressing ultimately to respiratory arrest. Aspirate for blood or cerebrospinal fluid (where applicable) prior to each dose and consider using a test dose. (5.5)

---------- 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. (7.2)

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

- Geriatric Use: Clinical studies and other reported clinical experience indicate that use of the drug in elderly patients requires a decreased dosage. Consider adjustment of dose. (8.5)
- Moderate to Severe Renal and/or Hepatic Impairment: Consider reduced dosage and increased monitoring for mepivacaine systemic toxicity. (8.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2023

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CARBOCAINE is indicated in adults and pediatric patients for the production of local or regional analgesia and/or anesthesia by local infiltration, peripheral nerve block techniques, and central neural techniques including epidural and caudal blocks. Specific concentrations and presentations of CARBOCAINE 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

CARBOCAINE is not intended for spinal anesthesia or dental use.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

- CARBOCAINE is not for intrathecal use.
- Carbocaine is supplied both with (multiple-dose vials) and without (single-dose vials) antimicrobial preservatives.
- Avoid use of CARBOCAINE solutions containing antimicrobial preservatives (i.e., multiple-dose vials) for epidural or caudal anesthesia *[see Warnings and Precautions (5.3)]*.
- 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. CARBOCAINE is a clear, colorless solution. Do not administer solutions which are discolored or contain particulate matter.
- Mixing or the prior or intercurrent use of any other local anesthetic with CARBOCAINE is not recommended because of insufficient data on the clinical use of such mixtures.

Administration Precautions

- CARBOCAINE is to be administered in carefully adjusted dosages by or under the supervision of experienced clinicians who are well versed in the diagnosis and management of dose-related toxicity and other acute emergencies which might arise from the block to be employed.
- Use CARBOCAINE 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 (5.1), 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 CARBOCAINE *[see Warnings and Precautions (5.1), Drug Interactions (7.1), Overdosage (10)]*.
- Avoid puncturing the skin if there are signs of inflammation and/or sepsis in the region of the proposed injection.

- Aspirate for blood or cerebrospinal fluid (where applicable) prior to injecting CARBOCAINE, 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 (5.5)]*.
- Avoid rapid injection of a large volume of CARBOCAINE 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 CARBOCAINE 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 CARBOCAINE

The dosage of CARBOCAINE 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.

Dosing in Adults

The types of block and recommended CARBOCAINE concentrations are shown in Table 1.

Table 1. Types of Block and Recommended CARBOCAINE Concentrations in Adults

Type of Block	1% (10 mg/mL)	1.5% (15 mg/mL)	2% (20 mg/mL)
Local infiltration*	✓		
Peripheral nerve block	✓		✓
Caudal block**	✓	✓	✓
Epidural block**	✓	✓	✓

* CARBOCAINE 0.5% (prepared via dilution) is also recommended for local infiltration.
** Avoid use of multiple-dose vials of CARBOCAINE for caudal or epidural anesthesia *[see Warnings and Precautions (5.3)]*.
✓= indicated use

The recommended single adult dosage (or the total of a series of doses given in one procedure) of CARBOCAINE for unsedated, healthy, normal-sized individuals should not usually exceed 400 mg. The recommended dosage is based on requirements for the average adult (see Table 2). The dosages in Table 2 are provided as a general guidance for use.

Do not exceed a total daily dosage of 1,000 mg in 24 hours because of slow accumulation of the anesthetic or its derivatives or slower than normal metabolic degradation or detoxification with repeat administration. While maximum doses of 7 mg/kg (550 mg) have been administered in some patients, these are not recommended, except in exceptional circumstances. Under no circumstances should the administration be repeated at intervals of less than 1.5 hours *[see Warnings and Precautions(5.1), Clinical Pharmacology (12.3)]*.

Table 2. Recommended Concentrations and Doses of CARBOCAINE for Adults

Procedure	Concentration	Total Dose	
		mL	mg
Cervical, brachial, intercostal nerve block	1% (10 mg/mL)	5 mL to 40 mL	50 mg to 400 mg
	2% (20 mg/mL)	5 mL to 20 mL	100 mg to 400 mg
Pudendal nerve block	1% (10 mg/mL)	2.5 mL to 20 mL administered on each side	25 mg to 200 mg administered on each side
	2% (20 mg/mL)	2.5 mL to 10 mL administered on each side	50 mg to 200 mg administered on each side
Transvaginal block (paracervical plus pudendal) *[see Use in Specific Populations (8.1)]*	1% (10 mg/mL)	up to 15 mL administered on each side	up to 150 mg administered on each side
Paracervical block[a] *[see Use in Specific Populations (8.1)]*	1% (10 mg/mL)	up to 10 mL administered on each side	up to 100 mg administered on each side
Caudal and epidural block[b] *[see Dosage and Administration (2.4)]*	1% (10 mg/mL)	15 mL to 30 mL	150 mg to 300 mg
	1.5% (15 mg/mL)	10 mL to 25 mL	150 mg to 375 mg
	2% (20 mg/mL)	10 mL to 20 mL	200 mg to 400 mg
Infiltration[c]	1% (10 mg/mL)	up to 40 mL	up to 400 mg
Therapeutic block (pain management)	1% (10 mg/mL)	1 mL to 5 mL	10 mg to 50 mg
	2% (20 mg/mL)	1 mL to 5 mL	20 mg to 100 mg

[a] This is the maximum recommended dose per 90-minute period in obstetrical and non-obstetrical patients. Inject slowly, 5 minutes between sides.

[b] Use only single-dose vials which do not contain a preservative.

[c] An equivalent amount of a 0.5% solution (prepared by diluting the 1% solution with Sodium Chloride Injection, USP) may be used for large areas.

Dosing in Pediatrics

The pediatric dose should be *carefully measured based on weight*, and should not exceed 5 mg/kg to 6 mg/kg in pediatric patients, especially those weighing less than 13.6 kg. In pediatric patients *under 3 years of age or weighing less than 13.6 kg* concentrations less than 2% (e.g., 0.5% to 1.5%) should be employed.

2.3 Use in Epidural Anesthesia

During the administration of epidural anesthesia, it is recommended that a test dose of CARBOCAINE without antimicrobial preservative be administered initially and the effects monitored before the full dose is given. When using a "continuous" catheter technique, test doses should be given prior to both the initial and all supplemental doses *[see Dosage and Administration (2.4)]*.

During epidural administration, administer CARBOCAINE solutions in incremental doses 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. Repeat doses should be preceded by a test dose containing epinephrine if not clinically contraindicated. Use only the single-dose vials for caudal or epidural anesthesia; avoid use of the multiple-dose vials for these procedures, which contain a preservative *[see Dosage and Administration (2.1, 2.4), Warnings and Precautions (5.3, 5.5)]*.

2.4 Test Dose for Caudal and Lumbar Epidural Blocks

CARBOCAINE without antimicrobial preservative is recommended for use as a test dose with epinephrine prior to caudal and lumbar epidural blocks when clinical conditions permit. An effective test dose should contain epinephrine (10 mcg to 15 mcg) to serve as a warning of unintended intravascular injection. The test dose should also contain 45 mg to 50 mg of CARBOCAINE to detect an unintended intrathecal administration. When using a "continuous" catheter technique, test doses should be given prior to both the original and all reinforcing doses, because plastic tubing in the epidural space can migrate into a blood vessel or through the dura. Closely monitor for early clinical signs of toxicity following each test dose *[see Warnings and Precautions (5.5)]*. Allot adequate time for onset of spinal block to detect possible intrathecal injection. An intravascular or intrathecal injection is still possible even if results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, high spinal, or cardiovascular effects from the epinephrine *[see Warnings and Precautions (5.1, 5.5), Overdosage (10)]*.

3 DOSAGE FORMS AND STRENGTHS

CARBOCAINE (mepivacaine hydrochloride) injection is a clear, colorless solution available as:

- 1% (300 mg/30 mL) (10 mg/mL) single-dose vials.
- 1% (500 mg/50 mL) (10 mg/mL) multiple-dose vials.
- 1.5% (450 mg/30 mL) (15 mg/mL) single-dose vials.
- 2% (400 mg/20 mL) (20 mg/mL) single-dose vials.
- 2% (1,000 mg/50 mL) (20 mg/mL) multiple-dose vials.

4 CONTRAINDICATIONS

CARBOCAINE is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type or to other components of solutions of CARBOCAINE.

5 WARNINGS AND PRECAUTIONS

5.1 Dose-Related Toxicity

The safety and effectiveness of CARBOCAINE depends 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 each injection of CARBOCAINE solution.

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, 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 CARBOCAINE that results in effective anesthesia to avoid high plasma levels and serious adverse effects.

Avoid rapid injection of a large volume of CARBOCAINE solution and administer fractional (incremental) doses when feasible.

Injection of repeated doses of CARBOCAINE may cause significant increases in plasma levels with each repeated dose due to slow accumulation of the drug or its metabolites or to slow metabolic degradation. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, and acutely ill patients should be given reduced doses commensurate with their age and physical status. Local anesthetics should also be used with caution in patients with severe disturbances of cardiac rhythm, shock, heart block, or hypotension.

5.2 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 (7.2)]*. 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 CARBOCAINE 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.

5.3 Antimicrobial Preservatives in Multiple-Dose Vials

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

5.4 Chondrolysis with Intra-Articular Infusion

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

5.5 Risk of Systemic Toxicities with Unintended Intravascular or Intrathecal Injection

Unintended intravascular or intrathecal injection of CARBOCAINE 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 CARBOCAINE, both the initial dose and all subsequent doses, to avoid intravascular or intrathecal injection. However, a negative aspiration for blood or cerebrospinal fluid does not ensure against an intravascular or intrathecal injection.

Use of Test Dose with Epidural Anesthesia

To serve as a warning of unintended intravascular or intrathecal injection, CARBOCAINE without antimicrobial preservative is recommended for use as a test dose with epinephrine prior to administration of the full dose in caudal and lumbar epidural blocks when clinical conditions permit *[see Dosage and Administration (2.4)]*. An effective test dose should contain epinephrine (10 mcg to 15 mcg) to serve as a warning of unintended intravascular injection. The test dose should also contain 45 mg to 50 mg of CARBOCAINE to detect an unintended intrathecal administration. An intravascular or intrathecal injection is still possible even if results of the test dose are negative.

Signs/symptoms of unintended intravascular or intrathecal injection of the test dose of CARBOCAINE with epinephrine and monitoring recommendations are described below.

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

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

5.6 Risk of Systemic Toxicity in Patients with Hepatic and/or Renal Impairment

Because amide-type local anesthetics such as mepivacaine are metabolized by the liver and excreted by the kidneys, consider reduced dosing and increased monitoring for mepivacaine systemic toxicity in patients with moderate to severe hepatic and/or renal impairment who are treated with CARBOCAINE, especially with repeat doses *[see Use in Specific Populations (8.6, 8.7)]*.

5.7 Risk of Use in Patients with Impaired Cardiovascular Function

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

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

Small doses of local anesthetics (e.g., CARBOCAINE) injected into the head and neck area, including retrobulbar and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care. Confusion, convulsions, respiratory depression, and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. They may also be due to puncture of the dural sheath of the optic nerve during retrobulbar block with diffusion of any local anesthetic along the subdural space to the midbrain. Monitor circulation and respiration and constantly observe patients receiving CARBOCAINE 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)]*.

5.9 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 CARBOCAINE), 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 (5.8)]*. 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.

6 ADVERSE REACTIONS

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

- Dose-Related Toxicity *[see Warnings and Precautions (5.1)]*
- Methemoglobinemia *[see Warnings and Precautions (5.2)]*
- Chondrolysis with Intra-Articular Infusion *[see Warnings and Precautions (5.4)]*
- Systemic Toxicities with Unintended Intravascular or Intrathecal Injection *[see Warnings and Precautions (5.5)]*

The following adverse reactions from voluntary reports or clinical studies have been reported with mepivacaine. 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 CARBOCAINE 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 countermeasures 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, and 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, heart block, hypotension (or sometimes hypertension), bradycardia, ventricular arrhythmias, and possibly cardiac arrest *[*see *Warnings and Precautions (5.5)]*.

Immune System Disorders

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

7 DRUG INTERACTIONS

7.1 Local Anesthetics

The toxic effects of local anesthetics are additive. If coadministration of other local anesthetics with CARBOCAINE 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 (5.1)]*.

7.2 Drugs Associated with Methemoglobinemia

Patients who are administered CARBOCAINE are at increased risk of developing methemoglobinemia when concurrently exposed to the following drugs, which could include other local anesthetics *[see Warnings and Precautions (5.2)]*:

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Local anesthetics including mepivacaine rapidly cross the placenta, and when used for epidural, paracervical, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, fetal, and neonatal toxicity *[see Clinical Considerations, see Clinical Pharmacology (12.3)]*. The incidence and degree of toxicity depend upon the procedure performed, the type, frequency, and amount of drug used, and the technique of drug

administration. Available data for mepivacaine use in pregnant women in early pregnancy are insufficient to establish a drug associated risk of major birth defects or miscarriage.

Animal reproduction studies have not been conducted with mepivacaine. Mepivacaine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see *Clinical Considerations*).

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

Clinical Considerations

Labor or Delivery

Adverse reactions in the parturient, fetus, and neonate involve alterations of the CNS, peripheral vascular tone, and cardiac function. Epidural, paracervical, 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.

Maternal Adverse Reactions

Maternal hypotension has resulted from regional anesthesia. 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 recommended maximum dose of the local anesthetic should not be exceeded. Injection should be made slowly and with frequent aspiration. Allow a five-minute interval between sides.

Fetal/Neonatal Adverse Reactions

There have been reports of fetal and neonatal deaths associated with administration of mepivacaine for paracervical and/or pudendal nerve blocks in pregnant women during delivery. Adhere to recommended dosages and proper administration techniques for these blocks. There have also been reports of fetal bradycardia, neonatal respiratory depression, and neonatal seizures after maternal administration of mepivacaine during delivery. Inadvertent direct injection into the fetus at delivery with serious outcomes, including death, have been described. The fetal heart rate should be monitored continuously, and electronic fetal monitoring is highly advisable.

Failure to achieve adequate analgesia with recommended doses should arouse suspicion of intravascular or fetal intracranial injection.

The use of some local anesthetic drug products during labor and delivery may be followed by diminished muscle strength and tone for the first day or two of life. The long-term significance of these observations is unknown.

8.2 Lactation

Risk Summary

There are no available data on the presence of mepivacaine in human milk, the effects on the breastfed infant, or the effect on milk production. Mepivacaine is structurally similar to bupivacaine; available data from case series and a case report demonstrate that bupivacaine is found in human milk at low levels. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CARBOCAINE

and any potential adverse effects on the breastfed child from CARBOCAINE or from the underlying maternal condition.

8.4 Pediatric Use

Recommendations of use for the administration of mepivacaine to pediatric patients are presented in *Dosage and Administration (2.2)*.

8.5 Geriatric Use

Clinical studies and other reported clinical experience indicate that use of the drug in elderly patients requires a decreased dosage.

Mepivacaine is metabolized primarily by the liver. Mepivacaine and mepivacaine metabolites are known to be substantially excreted by the kidney. Therefore the risk of adverse reactions including drug toxicities during use of this drug may be greater in patients with impaired hepatic and/or renal function. Because elderly patients are more likely to have decreased hepatic and/or renal function, care should be taken in dose selection, and it may be useful to monitor hepatic and/or renal function.

8.6 Hepatic Impairment

Amide-type local anesthetics, such as mepivacaine, 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 CARBOCAINE, especially with repeat doses *[see Warnings and Precautions (5.6), Use in Specific Populations (8.5), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Mepivacaine 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. Therefore, consider reduced dosing and increased monitoring for local anesthetic systemic toxicity in patients with moderate to severe renal impairment treated with CARBOCAINE, especially with repeat doses *[see Warnings and Precautions (5.6), Use in Specific Populations (8.5), Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Clinical Presentation

Acute emergencies from use of CARBOCAINE are generally related to high plasma levels encountered during therapeutic use or to unintended intrathecal injection *[see Warnings and Precautions (5.1, 5.5), Adverse Reactions (6)]*.

If not treated immediately, convulsions with simultaneous hypoxia, hypercarbia, and acidosis, plus myocardial depression from the direct effects of mepivacaine 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 CARBOCAINE 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 CARBOCAINE, consists of immediate attention to the establishment and maintenance of a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask. Endotracheal intubation, using drugs and techniques familiar to the clinician, may be indicated after initial administration of oxygen by

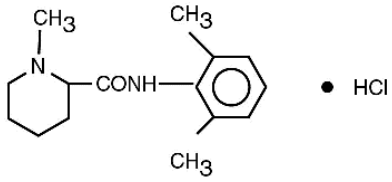
mask if difficulty is encountered in the maintenance of a patent airway, or if prolonged ventilatory support (assisted or controlled) is indicated.

If necessary, use drugs to manage the convulsions. A bolus intravenous dose of a benzodiazepine will counteract CNS stimulation related to CARBOCAINE. 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

CARBOCAINE contains mepivacaine hydrochloride, an amide local anesthetic, as the active pharmaceutical ingredient. The route of administration for CARBOCAINE is by injection, for local infiltration, peripheral nerve block, and caudal and lumbar epidural blocks. Multiple-dose vials contain methylparaben *[see Warnings and Precautions (5.3)]*.

Mepivacaine hydrochloride is 2-piperidinecarboxamide, *N*-(2,6-dimethylphenyl)-1-methyl, monohydrochloride. It is a white crystalline odorless powder, soluble in water, but very resistant to both acid and alkaline hydrolysis. It has the following structural formula:



$C_{15}H_{22}N_2O \cdot HCl$

CARBOCAINE (mepivacaine hydrochloride) is a clear and colorless sterile isotonic solution. Each mL of single-dose vial contains 10 mg, 15 mg or 20 mg of mepivacaine hydrochloride (equivalent to 8.71 mg, 13.07 mg, or 17.42 mg of mepivacaine, respectively) with the detailed composition shown in the table. Each mL of multiple-dose vial contains 10 mg or 20 mg of mepivacaine hydrochloride (equivalent to 8.71 mg or 17.42 mg of mepivacaine, respectively) with the detailed composition shown in the table.

Composition of Available Solutions*

	1% Single-Dose 30 mL Vial mg/mL	1% Multiple-Dose 50 mL Vial mg/mL	1.5% Single-Dose 30 mL Vial mg/mL	2% Single-Dose 20 mL Vial mg/mL	2% Multiple-Dose 50 mL Vial mg/mL
Mepivacaine hydrochloride	10	10	15	20	20
Sodium chloride	6.6	7	5.6	4.6	5
Potassium chloride	0.3		0.3	0.3	
Calcium chloride	0.33		0.33	0.33	
Methylparaben		1			1

*In Water for Injection.
The pH of the solution is adjusted between 4.5 and 6.8 with sodium hydroxide or hydrochloric acid.

The specific gravity of CARBOCAINE 1% at 25 °C is 1.007 for the single-dose vials and 1.008 for the multiple-dose vials. The specific gravity of CARBOCAINE 1.5% and 2% at 25 °C is 1.008.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mepivacaine 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 mepivacaine 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 and ultimately to cardiac arrest. 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 mepivacaine *[see Warnings and Precautions (5.5)]*.

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

The duration of anesthesia also varies depending upon the technique and type of block, the concentration, and the individual. Mepivacaine will normally provide anesthesia which is adequate for 2 to 2 1/2 hours of surgery.

A clinical study using 15 mL of 2% epidural mepivacaine at the T 9-10 interspace in 62 patients, 20-79 years of age, demonstrated a 40% decrease in the amount of mepivacaine required to block a given number of dermatomes in the elderly (60-79 years, N=13) as compared to young adults 20-39 years).

Another study using 10 mL of 2% lumbar epidural mepivacaine in 161 patients, 19-75 years of age, demonstrated a strong inverse relationship between patient age and the number of dermatomes blocked per cc of mepivacaine injected.

12.3 Pharmacokinetics

Systemic plasma levels of mepivacaine following administration of CARBOCAINE do not correlate with local efficacy.

Absorption

The rate of systemic absorption of mepivacaine 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 plasma concentration of mepivacaine, however, it has been reported that vasoconstrictors do not significantly prolong anesthesia with CARBOCAINE.

Distribution

Mepivacaine is approximately 75% bound to plasma proteins.

Mepivacaine 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 mepivacaine appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer. 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. Based on the pharmacokinetic analyses performed in several studies, mepivacaine is rapidly absorbed from the epidural space into the maternal blood stream and readily crosses the placenta as evidenced by detectable mepivacaine blood levels in the fetus as early as 5 minutes after anesthetic block administration. Fetal absorption and distribution of mepivacaine were noted in few cases that demonstrated tissue and organ levels of mepivacaine.

Depending upon the route of administration, mepivacaine 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.

Elimination

The half-life of CARBOCAINE in adults is 1.9 to 3.2 hours and in neonates 8.7 to 9 hours.

Metabolism

Mepivacaine is not detoxified by the circulating plasma esterases. The liver is the principal site of metabolism, with over 50% of the administered dose being excreted into the bile as metabolites. Most of the metabolized mepivacaine is probably resorbed in the intestine and then excreted into the urine since only a small percentage is found in the feces. It has been shown that hydroxylation and N-demethylation, which are detoxification reactions, play important roles in the metabolism of the anesthetic. Three metabolites of mepivacaine have been identified from human adults: two phenols, which are excreted almost exclusively as their glucuronide conjugates, and the N-demethylated compound (2′ 6′-pipecoloxylidide).

Excretion

The principal route of excretion is via the kidney. Most of the anesthetic and its metabolites are eliminated within 30 hours. It is rapidly metabolized, with only a small percentage of the anesthetic (5 to 10%) being excreted unchanged in the urine. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH.

Specific Populations

Patients with Hepatic Impairment

Various pharmacokinetic parameters of the local anesthetics including mepivacaine 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 including mepivacaine *[see Use in Specific Populations (8.5, 8.6)]*.

Patients with Renal Impairment

Various pharmacokinetic parameters of the local anesthetics including mepivacaine 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 mepivacaine hydrochloride have not been conducted.

Mutagenesis

The mutagenic potential of mepivacaine hydrochloride has not been determined.

Impairment of Fertility

The effect of mepivacaine hydrochloride 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.]

Single-dose vials and multiple-dose vials of CARBOCAINE may be sterilized by autoclaving at 15-pound pressure, 121 °C (250 °F) for 15 minutes. Solutions of CARBOCAINE may be reautoclaved when necessary.

CARBOCAINE (mepivacaine hydrochloride) injection is a clear, colorless solution. Do not administer solutions which are discolored or which contain particulate matter.

Unit of Sale and Product Description	Concentration
1% Contains 10 mg mepivacaine hydrochloride per mL	
NDC 0409-1036-30 Carton of 1 30 mL Single-Dose Vial	300 mg/30 mL (10 mg/mL)
NDC 0409-1038-50 Carton of 1 50 mL Multiple-Dose Vial	500 mg/50 mL (10 mg/mL)
1.5% Contains 15 mg mepivacaine hydrochloride per mL	
NDC 0409-1041-30 Carton of 1 30 mL Single-Dose Vial	450 mg/30 mL (15 mg/mL)
2% Contains 20 mg mepivacaine hydrochloride per mL	
NDC 0409-1067-20 Carton of 1 20 mL Single-Dose Vial	400 mg/20 mL (20 mg/mL)
NDC 0409-2047-50 Carton of 1 50 mL Multiple-Dose Vial	1,000 mg/50 mL (20 mg/mL)

For single-dose vials: Discard unused portion.

17 PATIENT COUNSELING INFORMATION

Allergic-Type Reactions

Assess if the patient has had allergic-type reactions to amide-type local anesthetics or to other formulation ingredients, such as the antimicrobial preservative methylparaben contained in multiple-dose vials *[see Contraindications (4), Adverse Reactions (6)]*.

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 (5.2)]*.

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.

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

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