PRODUCT MONOGRAPH

MARCAINE®
(Bupivacaine Hydrochloride Injection USP)
2.5 mg/mL, 5 mg/mL and 7.5 mg/mL

MARCAINE® SPINAL
(Bupivacaine Hydrochloride in Dextrose Injection USP)
7.5 mg/mL

MARCAINE® E
(Bupivacaine Hydrochloride and Epinephrine Injection USP)
Bupivacaine Hydrochloride 2.5 mg/mL and Epinephrine Bitartrate 9.1 mcg/mL
Bupivacaine Hydrochloride 5 mg/mL and Epinephrine Bitartrate 9.1 mcg/mL

Sterile Solution

Local Anesthetic

Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, Québec
H9J 2M5

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MARCAINE®
(Bupivacaine Hydrochloride Injection USP)

MARCAINE® SPINAL
(Bupivacaine Hydrochloride in Dextrose Injection USP)

MARCAINE® E
(Bupivacaine Hydrochloride and Epinephrine Injection USP)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Parenteral	MARCAINE (bupivacaine hydrochloride) Sterile Solution 2.5 mg/mL, 5 mg/mL and 7.5 mg/mL bupivacaine hydrochloride	Sodium chloride, sodium hydroxide and/or hydrochloric acid and water for injection. Multidose vials contain methylparaben as a preservative.
Parenteral	MARCAINE E (bupivacaine hydrochloride with epinephrine) Sterile Solution 2.5 mg/mL bupivacaine hydrochloride with epinepherine 1:200,000 (as bitartrate) 5 mg/mL bupivacaine hydrochloride with epinephrine 1:200,000 (as bitartrate)	Sodium chloride, sodium hydroxide and/or hydrochloric acid, monothioglycerol, ascorbic acid, sodium lactate 60% solution, edetate calcium disodium, sodium metabisulfite and water for injection.
Parenteral	MARCAINE SPINAL (bupivacaine hydrochloride) Sterile Solution 7.5 mg/mL bupivacaine hydrochloride , hyperbaric solution	Dextrose, sodium hydroxide and/or hydrochloric acid and water for injection.

INDICATIONS AND CLINICAL USE

Adults (> 18 years of age):

MARCAINE (bupivacaine hydrochloride), MARCAINE SPINAL (bupivacaine hydrochloride) and MARCAINE E (bupivacaine hydrochloride with epinephrine) are indicated for the production of local or regional anesthesia and analgesia with the following procedures:

- Local infiltration procedures
- Peripheral nerve blocks
- Retrobulbar blocks
- Caudal, epidural and subarachnoid (spinal) blocks

Standard procedures for local infiltration, minor and major nerve blocks, retrobulbar block or epidural block should be observed.

Geriatrics (> 65 years of age):
Elderly patients should be given reduced doses commensurate with their age and physical condition.

Pediatrics (< 2 years of age):
Until further experience is gained in children younger than two years, administration of any presentation of bupivacaine injection in this age group is not recommended.

CONTRAINDICATIONS

MARCAINE (bupivacaine hydrochloride), MARCAINE SPINAL (bupivacaine hydrochloride) and MARCAINE E (bupivacaine hydrochloride with epinephrine) are contraindicated:

- In patients with a hypersensitivity to bupivacaine, or to any local anesthetic agent of the amide type, or to other components of bupivacaine injections.

- For intravenous regional anesthesia (Bier Block) since unintentional leakage of bupivacaine over the tourniquet may cause systemic toxic reactions. Cardiac arrest and death have occurred (see **DOSAGE AND ADMINISTRATION**).

- In obstetric paracervical block anesthesia. Use of other local anesthetics in this technique has resulted in foetal bradycardia and death.

- In severe shock and in heart block and when there is inflammation and/or sepsis near the site of the proposed injection.

- MARCAINE parenteral solutions in multidose vials are contraindicated in patients with a known history of hypersensitivity to ester local anesthetics (which are metabolized to para

amino benzoic acid (PABA)), methylparaben and propylparaben (antimicrobial preservatives) or to their metabolite, PABA.

MARCAINE E (bupivacaine hydrochloride with epinephrine) is contraindicated in patients with a hypersensitivity to sodium metabisulfite (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**).

MARCAINE parenteral solutions in multidose vials contain methylparaben (antimicrobial preservative) and should not be used for epidural or spinal anesthesia, or for any route of administration that would introduce solution into the cerebrospinal fluid. The safety of these agents has not been established with regard to intrathecal injection, either intentional or accidental. These solutions should not be administered intra-ocularly or retro-ocularly.

Spinal Use

With the exception of serious diseases of the central nervous system or of the lumbar vertebral column, most anesthesiologists consider the following conditions to be only relative contraindications to spinal anesthesia. The decision as to whether or not spinal anesthesia should be used for an individual case depends on the physician's appraisal of the advantages, as opposed to the risks, and on his ability to cope with the complications that may arise.

1. Disease of the cerebrospinal system, such as meningitis, spinal fluid block, cranial or spinal hemorrhage, increased intracranial pressure, tumours and syphilis.

2. Shock. This should be treated before any anesthetic is administered. However, in emergency operations, spinal anesthesia may at times be considered the method of choice.

3. Profound anemia, cachexia and when death is imminent.

4. Sepsis with positive blood cultures.

5. High Blood Pressure. Spinal anesthesia should be well tolerated if particular care is taken to prevent a sudden or appreciable fall in blood pressure.

6. Low Blood Pressure. The use of suitable pressor agents and methods of controlling the diffusion of the anesthetic should remove the principal objection to spinal anesthesia in patients with low blood pressure.

7. Highly nervous and sensitive persons. Pre-operative medication should overcome this difficulty.

8. Visceral perforation, bowel strangulation, acute peritonitis. Some surgeons object to contraction of the gastrointestinal musculature; others, however, consider the associated arrest of peristalsis an advantage. With gastrointestinal hemorrhage, spinal anesthesia should be used with caution or may even be contraindicated.

9. Cardiac decompensation, massive pleural effusion and increased intra-abdominal pressure (e.g. full-term pregnancy, massive ascites, large tumor). High spinal anesthesia should not be used in patients with these conditions unless the Trendelenburg position can be omitted or the intra-abdominal pressure released slowly.

WARNINGS AND PRECAUTIONS

General

LOCAL ANESTHETICS SHOULD ONLY BE USED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MAY ARISE FROM THE BLOCK TO BE PERFORMED, AND THEN ONLY AFTER ENSURING THE IMMEDIATE AVAILABILITY OF CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, RESUSCITATIVE DRUGS, INCLUDING OXYGEN, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES (see **ADVERSE REACTIONS** AND **OVERDOSAGE**). 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.

THE HIGHEST (0.75%) CONCENTRATION OF ISOTONIC MARCAINE (BUPIVACAINE HYDROCHLORIDE) INJECTION IS NOT RECOMMENDED FOR OBSTETRICAL ANESTHESIA. THERE HAVE BEEN REPORTS OF CARDIAC ARREST WITH DIFFICULT RESUSCITATION OR DEATH FOLLOWING ITS USE FOR EPIDURAL ANESTHESIA IN OBSTETRICAL PATIENTS. RESUSCITATION HAS BEEN DIFFICULT OR IMPOSSIBLE DESPITE APPARENTLY ADEQUATE PREPARATION AND APPROPRIATE MANAGEMENT. CARDIAC ARREST HAS OCCURRED AFTER CONVULSIONS RESULTING FROM SYSTEMIC TOXICITY, PROBABLY FOLLOWING UNINTENTIONAL INTRAVASCULAR INJECTION.

AN INTRAVENOUS CANNULA MUST BE INSERTED BEFORE THE LOCAL ANESTHETIC IS INJECTED FOR NERVE BLOCKS WHICH MAY RESULT IN HYPOTENSION OR BRADYCARDIA, OR WHERE ACUTE SYSTEMIC TOXICITY MAY DEVELOP FOLLOWING INADVERTENT INTRAVASCULAR INJECTION.

THE LOWEST DOSAGE OF LOCAL ANESTHETIC THAT RESULTS IN EFFECTIVE ANESTHESIA OR ANALGESIA SHOULD BE USED TO AVOID HIGH PLASMA LEVELS AND SERIOUS ADVERSE REACTIONS. INJECTIONS SHOULD BE MADE SLOWLY OR IN INCREMENTAL DOSES, WITH FREQUENT ASPIRATIONS BEFORE AND DURING THE INJECTION TO AVOID INTRAVASCULAR INJECTION.

Reports of Irreversible Chondrolysis with Intra-articular Infusions of Local Anesthetics Following Surgery: Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of irreversible chondrolysis in patients receiving such infusions. The majority of reported cases of

irreversible chondrolysis have involved the shoulder joint; cases of gleno-humeral irreversible chondrolysis have been described in pediatric and adult patients following intraarticular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. 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 irreversible chondrolysis; patients who experienced irreversible chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement. MARCAINE (bupivacaine hydrochloride), MARCAINE SPINAL (bupivacaine hydrochloride) and MARCAINE E (bupivacaine hydrochloride with epinephrine) **should not be used for postoperative intra-articular infusion** (see **DOSAGE AND ADMINISTRATION**).

The following precautions apply to all local anesthetics: Select needles of proper length and bevel for the technique employed. Inject slowly with frequent aspirations and, if blood is aspirated, relocate the needle. Inadvertent intravascular injection may cause serious complications. Absorption is more rapid when injections are made into highly vascular tissues. In caudal or epidural anesthesia, abandon the method if the subarachnoid space has been entered, as shown by aspiration of spinal fluid. However, a negative aspiration is not 100% reliable.

Injection of repeated doses of bupivacaine may cause a significant increase in blood levels due to accumulation of the drug or its metabolites or slow metabolic degradation. Tolerance to elevated blood levels varies with the physical condition of the patient.

Major peripheral nerve blocks may imply the administration of a large volume of local anesthetic in areas of high vascularity, often close to large vessels where there is an increased risk of intravascular injection and/or rapid systemic absorption which can lead to high plasma concentrations.

Epinephrine-containing solutions should not be injected into tissues supplied by end arteries, for example, fingers and toes, ears, the nose, and the penis.

Local anesthetic procedures should be carried out sufficiently away from an inflamed region. Injections should not be performed through inflamed tissue or when there is sepsis at or near the injection site.

Cardiovascular

The decision to use a local anesthetic containing a vasoconstrictor in patients with peripheral vascular disease will depend on the physician's appraisal of the relative advantages and risks.

There have been reports of cardiac arrest or death during use of bupivacaine for epidural anesthesia or peripheral nerve blockade. In some instances, resuscitation has been difficult or impossible despite apparently adequate preparation and management.

Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported when bupivacaine was utilized for local anesthetic procedures that may have resulted in high systemic concentrations of bupivacaine.

Epidural anesthesia or analgesia may lead to hypotension and bradycardia. The risk of such effects can be reduced either by preloading the circulation with crystalloidal or colloidal solutions or by injecting a vasopressor such as ephedrine 20-40 mg intramuscularly. Hypotension should be treated promptly, e.g., with ephedrine 5-10 mg intravenously and repeated as necessary. Children should be given ephedrine doses commensurate with their age and weight.

MARCAINE E (bupivacaine hydrochloride with epinephrine) should be used with caution in patients who may have severe or untreated hypertension, ischemic heart disease, cerebral vascular insufficiency, heart block, peripheral vascular disorder and any other pathological condition that might be aggravated by the effects of epinephrine.

Local anesthetics should be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by amide-type local anesthetics.

Patients with partial or complete heart block require special attention since local anesthetics may depress myocardial conduction. To reduce the risk of potentially serious adverse reactions, attempts should be made to optimize the patient's condition before major blocks are performed. Dosage should be adjusted accordingly.

Central nerve blocks may cause cardiovascular depression, especially in the presence of hypovolemia. Epidural anesthesia should be used with caution in patients with impaired cardiovascular function.

Endocrine

MARCAINE E (bupivacaine hydrochloride with epinephrine) should be used with caution in patients whose medical history and physical evaluation suggest the existence of poorly controlled hyperthyroidism or advanced diabetes.

Spinal Use

In addition to the above noted precautions, when administering bupivacaine hyperbaric solution for spinal anesthesia, the patient's blood pressure should be carefully monitored. Spinal anesthesia is usually associated with a fall in arterial blood pressure due to sympathetic blockade.

Epidural Use

It is recommended that a test dose be administered initially and the effects monitored before the full dose is given (also see **DOSAGE AND ADMINISTRATION**). Generally, 2 to 3 mL of 0.5% bupivacaine containing 1:200,000 epinephrine, when clinical conditions permit, should be administered to check that the spinal canal or a blood vessel has not been entered while locating the epidural needle or catheter. In the event of a spinal injection, clinical signs of spinal block would become evident in a few minutes. In the event of intravascular injection, a transient increase in pulse rate and/or systolic blood pressure is usually detectable with a monitor. The other symptoms and signs of "epinephrine response" are less dependable. Concomitantly administered medications may modify these responses. When reinforcing doses are required, the test dose should be used again to check the catheter location. However, an intravascular or subarachnoid injection is still possible even if results of the test dose are negative. Patients on

beta-blockers may not manifest changes in heart rate, but blood pressure monitoring can detect an evanescent rise in systolic blood pressure.

During epidural administration, bupivacaine should be administered in incremental doses, with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Frequent aspirations for blood or cerebrospinal fluid (where applicable, *i.e.*, when using a "continuous" intermittent catheter technique), should be performed before and during each supplemental injection because plastic tubing in the epidural space can migrate into a blood vessel or through the dura. A negative aspiration, however, does not ensure against an intravascular or intrathecal injection.

Injection in Head and Neck Area

Relatively small doses of local anesthetics 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 leading to cardiac arrest 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. Patients receiving these blocks should remain under constant observation and monitoring for their cardiac and pulmonary functions. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded (see **DOSAGE AND ADMINISTRATION**).

Ophthalmic Surgery

Retrobulbar injections may very occasionally reach the cranial subarachnoid space causing temporary blindness, cardiovascular collapse, apnoea, convulsions, etc. These reactions, which may be due to intra-arterial injection or direct injection into the central nervous system via the sheaths of the optic nerve, must be diagnosed and treated promptly.

Clinicians who perform retrobulbar blocks should be aware that there have been reports of respiratory arrest following local anesthetic injection. Prior to retrobulbar block, as with all other regional procedures, the immediate availability of equipment, drugs, and personnel to manage respiratory arrest or depression, convulsions, and cardiac stimulation or depression should be assured (see also **WARNINGS AND PRECAUTIONS**, **Injection in Head and Neck Area**). 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 conjunctivia.

When 0.75% bupivacaine 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.

Retrobulbar injections of local anesthetics carry a low risk of persistent ocular muscle dysfunction. The primary causes include trauma and/or local toxic effects on muscles and/or nerves. The severity of such tissue reactions is related to the degree of trauma, the concentration of the local anesthetic and the duration of exposure of the tissue to the local anesthetic. For this reason, as with all local anesthetics, the lowest effective concentration and dose of local anesthetic should be used. Vasoconstrictors and other additives may aggravate tissue reactions and should be used only when indicated.

Hepatic

Because amide-type local anesthetics such as bupivacaine are metabolized by the liver, these drugs should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations.

Peri-Operative Considerations

It is essential that aspiration for blood or cerebrospinal fluid be done prior to injecting any local anesthetic, both the original dose and all subsequent doses, to avoid intravascular or subarachnoid injection. During the performance of spinal anesthesia, a free flow of cerebrospinal fluid is indicative of entry into the subarachnoid space. Aspiration should be performed before the anesthetic solution is injected to confirm entry into the subarachnoid space and to avoid intravascular injection. However, a negative aspiration does not ensure against an intravascular or subarachnoid injection.

The safety and effectiveness of local anesthetics depend on proper dosage, correct technique, adequate precautions and readiness for emergencies. Regional or local anesthetic procedures should always be performed in a properly equipped and staffed area.

Resuscitative equipment and resuscitative drugs, including oxygen, should be available for immediate use (see **WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS** and **OVERDOSAGE**). During major regional nerve blocks, the patients should be in an optimal condition and have intravenous fluids running via an indwelling catheter to assure a functioning intravenous pathway. The clinician responsible should have adequate and appropriate training in the procedure to be performed, should take the necessary precautions to avoid intravascular injection (see **DOSAGE AND ADMINISTRATION**), and should be familiar with the diagnosis and treatment of side effects, systemic toxicity and other complications (see **ADVERSE REACTIONS** and **OVERDOSAGE**).

Careful and constant monitoring of cardiovascular and respiratory vital signs (adequacy of ventilation) and the patient's state of consciousness should be performed after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus,

dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.

Renal
Local anesthetics should be used with caution in patients in poor general condition due to severe renal dysfunction although regional anesthesia is frequently indicated in these patients.

Hyper-Sensitivity
MARCAINE E (bupivacaine hydrochloride with epinephrine) contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

MARCAINE parenteral solutions in multidose vials are contraindicated in patients with known hypersensitivities to local anesthetics of the amide type, to other components in the formulation, parabens and their metabolite para amino benzoic acid (PABA). The use of paraben-containing bupivacaine preparations should also be avoided in patients who are allergic to ester local anesthetics (see **CONTRAINDICATIONS**).

Special Populations
Debilitated and acutely ill patients should be given reduced doses commensurate with their age and physical condition.

Pregnant Women: Decrease pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine hydrochloride was administered to these species in doses comparable, respectively, to nine and five times the maximal recommended daily human dose (400 mg).

There are no adequate and well-controlled studies in pregnant women of the effect of bupivacaine on the developing foetus.

Bupivacaine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. This does not exclude the use of bupivacaine at term for obstetrical anesthesia or analgesia.

Labour and Delivery: The highest (0.75%) isotonic concentration is not recommended for obstetrical anesthesia (see **WARNINGS AND PRECAUTIONS**). This, however, does not exclude the use of isotonic Marcaine 0.25% or 0.5% or the spinal use of the hyperbaric Marcaine 0.75% in dextrose at term for obstetrical anesthesia or analgesia.

Bupivacaine is contraindicated for obstetrical paracervical block anesthesia (see **WARNINGS AND PRECAUTIONS**). Local anesthetics rapidly cross the placenta, and when used for epidural, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, foetal and neonatal toxicity. 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, foetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

Maternal hypotension has resulted from regional anesthesia (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular**). Local anesthetics produce vasodilation by blocking sympathetic nerves. It is extremely important to avoid aortocaval compression by the gravid uterus during administration of regional block to parturients. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The foetal heart rate also should be monitored continuously, and electronic foetal monitoring is highly advisable.

Epidural 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 labour by removing the parturient's urge to bear down or by interfering with motor function. The use of MARCAINE 0.25% has been shown to interfere less than the 0.5% solution. Obstetrical anesthesia may increase the need for forceps assistance.

The addition of epinephrine may potentially decrease uterine blood flow and contractility, especially after inadvertent injection into maternal blood vessels.

Nursing Women: Bupivacaine is excreted in the breast milk, but in such small quantities that there is generally no risk of affecting the infant at therapeutic doses. It is not known whether epinephrine enters breast milk or not, but it is unlikely to affect the breast-fed infant.

Pediatrics: Until further experience is gained in children younger than two years, administration of any presentation of bupivacaine injection in this age group is not recommended.

Until further experience is gained, the following restrictions apply to the use of MARCAINE: (a) isotonic bupivacaine solutions with or without epinephrine are not recommended for spinal use; (b) the 0.75% isotonic solution of bupivacaine without epinephrine is not recommended in patients younger than 12 years; (c) MARCAINE SPINAL (bupivacaine hydrochloride 0.75% hyperbaric solution in dextrose) is not recommended for spinal use in patients younger than 18 years.

Geriatrics: Elderly patients should be given reduced doses commensurate with their age and physical condition.

ADVERSE REACTIONS

Reactions to bupivacaine hydrochloride are characteristic of those associated with other local acting anesthetics of the amide type.

Adverse reactions to local anesthetics are very rare in the absence of overdose or inadvertent intravascular injection. The effects of systemic overdose and unintentional intravascular injections can be serious, but should be distinguished from the physiological effects of the nerve block itself (e.g. a decrease in blood pressure and bradycardia during epidural anesthesia).

Neurological damage, caused directly (e.g. nerve trauma) or indirectly (e.g. epidural abscess) by the needle puncture, is a rare but well recognised consequence of regional, and particularly epidural anesthesia.

The most commonly encountered acute adverse experiences that demand immediate management are related to the central nervous system and the cardiovascular system. These adverse reactions are generally dose-related and due to high plasma levels which may result from overdosage (see **OVERDOSAGE**), rapid absorption from the injection site, diminished tolerance or from inadvertent intravascular injection. Factors influencing plasma protein binding, e.g. diseases which alter protein synthesis or competition of other drugs for protein binding, may diminish individual tolerances.

In addition to systemic dose-related toxicity, unintentional subarachnoid 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) may result in underventilation or apnoea ("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 may occur. This may lead to secondary cardiac arrest if untreated.

Central Nervous System: These are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, paraesthesia, numbness of the tongue, hyperacousis, lightheadedness, dysarthria and constriction of the pupils.

Cardiovascular System: High doses or unintentional intravascular injection may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, heart block, hypotension, bradycardia, hypertension, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and cardiac arrest. Reactions due to systemic absorption may be either slow or rapid in onset. Cardiovascular collapse and cardiac arrest can occur rapidly (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular** and **OVERDOSAGE**).

Allergic: Allergic type reactions are rare (<0.1%) and may occur as a result of sensitivity to local anesthetics of the amide type. These reactions are characterized by signs such as urticaria, pruritis, erythema, angioneurotic oedema (including laryngeal oedema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and in the most severe instances, anaphylactic shock.

Neurologic: The incidence of adverse neurologic reactions may be related to the total dose of local anesthetic administered but is also dependent upon the particular drug used, the route of administration and the physical condition of the patient. Nerve trauma, neuropathy, urinary retention, diplopia and spinal cord dysfunction (e.g., anterior spinal artery syndrome, arachnoiditis, cauda equina syndrome, in rare cases paresis and paraplegia), have been associated

with regional anesthesia. Neurological effects may be related to local anesthetic techniques, with or without a contribution from the drug.

High or Total Spinal Blockade: In the practice of caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter may occur, resulting in High or Total Spinal Blockage. Subsequent adverse effects may depend partially on the amount of drug administered subdurally.

Extensive loss of motor and sensory functions, loss of consciousness and cardiovascular and respiratory depression may happen. The cardiovascular depression is caused by extensive sympathetic blockade which may result in profound hypotension and bradycardia, or even cardiac arrest. Respiratory depression is caused by blockade of the innervation of the respiratory muscles, including the diaphragm.

Spinal Use: THE MOST COMMONLY ENCOUNTERED ADVERSE REACTIONS WHICH DEMAND IMMEDIATE COUNTERMEASURES ARE HYPOTENSION DUE TO LOSS OF SYMPATHETIC TONE AND RESPIRATORY PARALYSIS OR UNDERVENTILATION DUE TO CEPHALAD EXTENSION OF THE MOTOR LEVEL OF ANESTHESIA. THESE MAY LEAD TO CARDIAC ARREST IF UNTREATED.

In addition, one or several of the following complications or side effects may be observed during or after spinal anesthesia.

Meningitis
With the employment of an aseptic technique, septic meningitis should be practically nonexistent. Some instances of aseptic meningitis, with fever, neck rigidity, and cloudy spinal fluid, have been reported with the use of other spinal anesthetics. In such cases, the course is usually brief and benign, terminating in complete recovery.

However, in a few, permanent paralyses (sometimes terminating fatally) and sensory disturbances have been observed. This type of meningitis has also been observed in rare instances following ordinary diagnostic lumbar puncture.

Palsies
These are rare and affect either the extraocular muscles or the legs and the anal and vesical sphincters (cauda equina syndrome). Paralysis of extraocular muscles usually clears up spontaneously by the third or fourth week.

Clauda equina and lumbosacral cord complications (usually consisting of arachnoiditis and demyelinization) result in either loss or impairment of motor and sensory function of the saddle area (bladder, rectum) and one or both legs. The complications have occurred after the use of most, if not all, spinal anesthetics. The loss or impairment of motor function may be permanent or partial recovery may slowly occur. Various explanations for such complications have been advanced, such as hypersensitivity or intolerance to the anesthetic agent with a resultant myelolytic or neurotoxic effect; pooling of relatively high concentrations of anesthetic solution around the cauda equina and spinal cord before diffusion; and accidental injection of irritating

antiseptics or detergents (as when syringes and needles are incompletely cleansed or when ampoule storage enters a cracked ampoule). Hence, most anesthesiologists prefer to autoclave ampoules in order to destroy bacteria on the exterior before opening.

Headache
This may largely be prevented by using a small gauge needle to prevent spinal fluid leakage and by placing the patient in the supine position after operation and providing adequate hydration.

Nausea and Vomiting
These may be due to a drop in blood pressure, undue intra-abdominal manipulation or pre-operative medication.

DRUG INTERACTIONS

Drug-Drug Interactions

See **WARNINGS AND PRECAUTIONS** concerning solutions containing a vasoconstrictor.

Bupivacaine should be used cautiously in persons with known drug allergies or sensitivities.

Local anesthetics
Mixing or the prior or intercurrent use of any other local anesthetic with bupivacaine is not recommended because of insufficient data regarding the interaction and safety of such mixtures. Bupivacaine should be used with caution in patients receiving other amide-type local anesthetics such as lidocaine, ropivacaine, mepivacaine and prilocaine since the toxic effects are additive.

Antiarrhythmic Drugs
Bupivacaine should also be used with caution with structurally related agents such as the antiarrhythmics, procainamide, disopyramide, tocainide, mexiletine and flecainide.

Class III Antiarrhythmic drugs
Specific interaction studies with bupivacaine and class III anti-arrhythmic drugs (e.g. amiodarone) have not been performed, but caution is advised. Patients being treated with class III anti-arrhythmic drugs should be under close surveillance and ECG monitoring since cardiac affects may be additive.

Ergot-Containing Drugs
Bupivacaine with epinephrine or other vasopressors or vasoconstrictors should not be used concomitantly with ergot-type oxytocic drugs, because a severe persistent hypertension may occur and cerebrovascular and cardiac accidents are possible.

Monoamine Oxidase (MAO) Inhibitors
The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors may produce severe, prolonged hypertension.

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

Tricyclic Antidepressants (triptyline, imipramine)
The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving tricyclic antidepressants may produce severe, prolonged hypertension. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, extreme caution and careful patient monitoring is essential.

Neuroleptics (phenothiazines, butyrophenones)
Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine resulting in hypotensive responses and tachycardia.

Sedatives
If sedatives are used to reduce patient apprehension, they should be used in reduced doses, since local anesthetic agents, like sedatives, are central nervous system depressants which in combination may have an additive effect.

General Anesthetics- Inhalation agents (halothane, cyclopropane, trichloroethylene, enflurane and related agents)
Dose-related cardiac arrhythmias may occur if preparations containing epinephrine are employed in patients during or immediately following the administration of general anesthesia with inhalational agents such as halothane, cyclopropane, trichloroethylene, enflurane or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vascoconstrictor used, and the time since injection, when applicable, should be taken into account.

Use of chloroprocaine or other local anesthetics, prior to general anesthesia, may interfere with subsequent use of bupivacaine. Because of this, and because safety of intercurrent use with bupivacaine and other local anesthetics has not been established, such use is not recommended.

H_2-antagonists
The H_2-antagonists cimetidine and ranitidine have been shown to reduce the clearance of bupivacaine; ranitidine to a lesser degree than cimetidine. Concomitant administration may increase likelihood of toxicity of bupivacaine. Administration of H_2 blockers prior to epidural anesthesia is inadvisable since toxic levels of local anesthetic may result.

Non-selective beta-blockers
Non-selective beta-blockers such as propranolol enhance the pressor effects of epinephrine, which may lead to severe hypertension and bradycardia.

Drug-Food Interactions
Interactions of bupivacaine with food have not been established.

Drug-Herb Interactions
Interactions of bupivacaine with herbal products have not been established.

Drug-Laboratory Interactions
Interactions of bupivacaine with laboratory tests have not been established.

Drug-Lifestyle Interactions
Interactions of bupivacaine with lifestyle have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

General

As with all local anesthetics, the dosage of bupivacaine varies and depends upon 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, individual tolerance, the technique of anesthesia and the physical condition of the patient. The lowest dosage and concentration needed to provide effective anesthesia should be administered. The rapid injection of a large volume of local anesthetic solution should be avoided and fractional doses should be used when feasible. In general, complete block of all nerve fibers in large nerves requires the higher concentrations of drug. In smaller nerves, or when a less intense block is required (*e.g.*, in the relief of labour pain), the lower concentrations are indicated. The volume of drug used will affect the extent of spread of anesthesia.

The use of bupivacaine with epinephrine will prolong the anesthetic action.

In recommended doses, bupivacaine produces complete sensory block, but the effect on motor function differs among the three concentrations.

- 0.25%, when used for caudal, epidural, or peripheral nerve block, produces incomplete motor block. Should be used for operations in which muscle relaxation is not important, or when another means of providing muscle relaxation is used concurrently. Onset of action may be slower than with the 0.5% or 0.75% solutions.

- 0.5% provides motor blockade for caudal, epidural, or nerve block, but muscle relaxation may be inadequate for operations in which complete muscle relaxation is essential.

- 0.75% produces complete motor block. This concentration is recommended only for epidural block (single dose) in abdominal operations requiring complete muscle relaxation without the aid of other medication, and for retrobulbar anesthesia. It is not recommended for epidural block in obstetrical patients.

There have been adverse event reports of irreversible chondrolysis in patients receiving intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures.
MARCAINE (bupivacaine hydrochloride), MARCAINE SPINAL (bupivacaine hydrochloride)

and MARCAINE E (bupivacaine hydrochloride with epinephrine) is not approved for this use (see **WARNINGS AND PRECAUTIONS**, **General**).

Special Populations
Local anesthetics should be used with caution in patients in poor general condition due to aging or other compromising factors such as advanced liver disease or severe renal dysfunction although regional anesthesia is frequently indicated in these patients.

Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with their age and physical condition.

Recommended Dose and Dosage Adjustment

The duration of anesthesia with bupivacaine is such that, for most procedures, a single dose is sufficient. Maximum dosage limit must be individualized in each case after evaluating the size and physical status of the patient, as well as the usual rate of systemic absorption from a particular injection site. Most experience to date is with single doses of bupivacaine up to 225 mg with epinephrine 1:200,000 and 175 mg without epinephrine; more or less drug may be used depending on individualization of each case. The maximum doses of bupivacaine are considered to apply to a healthy 70 kilogram, young male. However, it is not recommended that they be exceeded in heavier persons.

At present, there is insufficient clinical evidence with multiple dosage or intermittent dose techniques to permit precise recommendations for such procedures to be given. However, limited clinical experience in this area of use indicates that bupivacaine may be repeated in 3 to 6 hours; total daily doses have been up to 400 mg. The duration of anesthetic effect may be prolonged by the addition of a vasoconstricting substance, e.g. epinephrine.

The 0.75% concentration of isotonic MARCAINE (bupivacaine hydrochloride) is not recommended for obstetrical anesthesia or analgesia (see **WARNINGS AND PRECAUTIONS**). The 0.5% and 0.25% concentrations of isotonic MARCAINE and the 0.75% hyperbaric solution of MARCAINE in dextrose are recommended at term for obstetrical anesthesia and analgesia.

When prolonged blocks are used, the risks of reaching a toxic plasma concentration or inducing a local neural injury must be considered. The maximum dosage limit must be determined by evaluating the size and physical condition of the patient and considering the usual rate of systemic absorption from a specific injection site. Experience to date indicates that 400 mg administered over 24 hours is well tolerated in average adults. Until further experience is gained, this dose should not be exceeded in 24 hours.

To avoid intravascular injection, aspiration should be repeated prior to and during administration of the main dose, which should be injected slowly or in incremental doses, at a rate of 25-50 mg/min, while closely observing the patient's vital functions and maintaining verbal contact. An inadvertent intravascular injection may be recognized by a temporary increase in heart rate and

an accidental intrathecal injection by signs of a spinal block. If toxic symptoms occur, the injection should be stopped immediately.

Adults:
The following table is presented as a guide to the use of bupivacaine in adults. The doses shown have generally proved satisfactory for the average patient. They may require reduction in relation to age and the physical condition of the patient. The clinician's experience and knowledge of the patient's physical condition are of importance in calculating the required dose.

Table 1 Dosage recommendations in adults

TYPE OF BLOCK	CONC. (%)	EACH DOSE[a] mL	mg	ONSET (min.)	DURATION (h) Without epinephrine	INDICATION
Local infiltration	0.25 0.5	up to 60[b] up to 30[b]	up to 150[b] up to 150[b]	1-3 1-3	3-4 4-8	Surgical operations and postoperative analgesia.
Epidural	0.5[c]	3-5	15-25			Test dose.
Lumbar epidural	0.25 0.5	6-15 15-30	15-37.5 75-150	2-5 15-30	1-2 2-3	Labour and postoperative pain relief. Surgical operations including Caesarean Section.
Thoracic epidural	0.25 0.5	5-15 5-10	12.5-37.5 25-50	10-15 10-15	1.5-2 2-3	Surgical operations.
Caudal epidural	0.25 0.5	20-30 20-30	50-75 100-150	20-30 15-30	1-2 2-3	Pain relief and diagnostic use. Surgical operations and postoperative analgesia.
Intercostal (per nerve)	0.5	2-3	10-15	3-5	4-8	Pain relief for surgery, postoperative and trauma.
Brachial Plexus	0.5	30	150	15-30	4-8	Surgical operations.
Sciatic	0.5	10-20	50-100	15-30	4-8	Surgical operations.
Digital[d]	0.25	1-5	2.5-12.5	2-5	3-4	Surgical operations.
Peripheral nerves	0.25 0.5	up to 40[b] up to 30[b]	up to 100[b] up to 150[b]	10-20 5-10	3-5 4-8	Therapeutic (pain relief). Surgical operations.
Sympathetic[e] Stellate block Lumbar Paravertebral block Coeliac plexus block	0.25 0.25 0.25	5-15 10-20 20-40	12.5-37.5 25-50 50-100	10-20 10-20 10-20	3-6 3-6 3-6	Ischemic conditions or sympathetic maintained pains *e.g.*, visceral pain conditions such as pancreatitis or cancer, pain of herpes zoster.

a For epidural blocks, dose includes test dose.
b No more than 400 mg in 24 hours. There have been post-marketing reports of irreversible chondrolysis in patients receiving post-operative intra-articular infusion of local anesthetics. MARCAINE, MARCAINE SPINAL and MARCAINE E are not approved for this use (see **WARNINGS AND PRECAUTIONS**, **General**).
c With epinephrine 1:200,000 (5 mcg/mL).
d Without epinephrine.
e See **WARNINGS AND PRECAUTIONS**

Children:

Until further experience is gained, bupivacaine is not recommended for children younger than two years of age. The following restrictions apply to the use of MARCAINE (bupivacaine

hydrochloride), MARCAINE E (bupivacaine hydrochloride with epinephrine) and MARCAINE SPINAL (bupivacaine hydrochloride) for children over two years of age: (a) isotonic bupivacaine solutions with or without epinephrine are not recommended for spinal use; (b) the 0.75% isotonic solution of bupivacaine without epinephrine is not recommended in patients younger than 12 years; (c) MARCAINE SPINAL (bupivacaine hydrochloride 0.75% hyperbaric solution in dextrose) is not recommended for spinal use in patients younger than 18 years.

For bolus administration or intermittent injections, unless stated otherwise (see Table 2), a dose of up to 2 mg/kg of bupivacaine or bupivacaine with epinephrine is recommended. The dose administered will depend on the age and body weight of the patient, the site of surgery, and the condition of the patient. The addition of epinephrine will prolong the duration of the block by 50-100%. For the appropriate suggested concentrations and dosage, see the following table:

Table 2 Dosage recommendations in children (over two years of age) for bupivacaine with and without epinephrine-isotonic solutions

Type of Block	**Conc (%)**	**each dose**	
		mL/kg	**mg/kg**
local infiltration	0.25	up to 0.8	up to 2
	0.5	up to 0.4	up to 2
Caudal epidural[c] -Lumbosacral -Thoracolumbar	 0.25 0.25	 0.5 0.6- 1.0	 1.25[d] 1.5- 2.5[d]
Lumbar epidural	0.25 0.5	0.5-1.0 0.3-0.5	1.25- 2.5 1.5-2.5
Dorsal (penile)	0.25[a] 0.5[a]	0.1-0.2 0.1-0.2	0.25-0.5 0.5-1.0
Intercostal	0.25[b] 0.5[b]	0.8-1.2 0.4-0.6	2-3 2-3

NOTE: The use of bupivacaine with and without epinephrine for anesthesia and/or analgesia may be supplementary to light general anesthesia

[a] Without epinephrine

[b] With epinephrine 1:200,000 (5 mcg/mL)

[c] Consider both age and weight for calculation of dosages

[d] Onset: 20-30 minutes, Duration: 2-6 hours

Use in Epidural Anesthesia

When an epidural dose is to be injected, a test dose of a local anesthetic is recommended (see **WARNINGS AND PRECAUTIONS**). MARCAINE E 0.5% (bupivacaine with epinephrine), or 3-5 mL lidocaine (Xylocaine® 1-2%) with epinephrine, can be used if a vasoconstrictor is not contraindicated. Verbal contact and repeated monitoring of heart rate and blood pressure should be maintained for five minutes after the test dose. In the absence of signs of subarachnoid or intravascular injection, the main dose may be given.

During epidural administration, bupivacaine should be administered slowly in incremental doses of 3 to 5 mL, with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection.

Solutions in multidose vials contain methylparaben (antimicrobial preservative) and should not be used since their safety has not been established (see **CONTRAINDICATIONS**).

Spinal Use

Bupivacaine for spinal anesthesia is available as a 0.75% hyperbaric solution.

The smallest dose required to produce the desired result should be administered and the dosage should be reduced for elderly and debilitated patients and patients with cardiac and/or liver disease. The use of the hyperbaric solution should permit improved control of the extent of anesthesia since the solution will have a higher specific gravity than spinal fluid.

Bupivacaine in dextrose (0.75% hyperbaric solution) is not recommended in patients younger than 18 years of age.

RECOMMENDED ADULT DOSAGE LIMITS FOR SPINAL ANESTHESIA			
Extent of Anesthesia	**Bupivacaine 0.75% Hyperbaric Solution Dosage**		**Injection Site (Lumbar Interspace)**
	mL	**mg**	
Low Spinal and Saddle block for perineal operations	0.8 - 1.06	6 - 8	4th
Median Spinal for operations on lower abdomen	1.06 - 1.6	8 - 12	3rd or 4th
High Spinal for operations on upper abdomen	1.6 - 2.0	12 - 15	2nd, 3rd or 4th

Solutions in multidose vials contain methylparaben (antimicrobial preservative) and should not be used for epidural or spinal anesthesia or for any route of administration that would introduce solution into the cerebrospinal fluid. Local anesthetic solutions containing antimicrobial preservatives solutions should not be administered intra-ocularly or retro-ocularly. These solutions should not be used in doses greater than 15mL for other types of blockades (see **CONTRAINDICATIONS**).

The extent and degree of spinal anesthesia depend on: the dose of anesthetic (see table), the specific gravity of the anesthetic solution, the volume of solution administered, the force of injection, the level of puncture and the position of the patient during and immediately after injection.

The lateral recumbent position is the customary one for injection; however, when both perineal and abdominal anesthesia are required, the sitting position may be preferred. After preliminary antiseptic preparation of the back, the spinal interspace to be punctured is marked and anesthetized with 1 to 2 mL of 0.25% bupivacaine HCl solution.

Ephedrine (25 mg) may be administered if needed to maintain blood pressure.

After the spinal anesthetic has been administered, the specific gravity of the solution injected determines which position the patient should be placed in, at least for the first 15 to 20 minutes. Continuous sensory tests should be made by gentle strokes with a sharp instrument or by pinching the skin, comparing the sensitivity to that of the inside of the forearm.

Since hypalgesia always precedes anesthesia, it is necessary to determine the line of demarcation between hypalgesia and normal sensation, to avoid extension of anesthesia above the desired segment.

After injection of a 0.75% hyperbaric solution for spinal anesthesia, the patient is immediately placed on his back and the table tilted to a 10 to 20 degree Trendelenburg position in order to allow the solution to flow cephalad.

Under no circumstances should a patient be left in a head-down position longer than one minute from the start of injection without testing the height of anesthesia. The neck is sharply flexed by supporting the head on a double pillow. When hypalgesia is extended to the desired height, the table is promptly brought to the horizontal position and time (about 10 to 20 minutes) allowed for the anesthetic agent to become fixed.

OVERDOSAGE

Acute systemic toxicity from local anesthetics is generally related to high plasma levels encountered during therapeutic use of local anesthetics, or to unintended subarachnoid or intravascular injection, exceptionally rapid absorption from highly vascularized areas or overdosage and originates mainly in the central nervous and the cardiovascular systems (see **ADVERSE REACTIONS** and **WARNINGS AND PRECAUTIONS**). Central nervous system reactions are similar for all amide local anesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively.

Symptoms

Accidental intravascular injections of local anesthetics may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, systemic toxicity appears later (15-60 minutes after injection) due to the slower increase in local anesthetic blood concentration.

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are usually circumoral paresthesia, numbness of the tongue, lightheadedness, hyperacousis, tinnitus and visual disturbances. Dysarthria, muscular twitching or tremors are more serious and precede the onset of generalized convulsions. These signs must

not be mistaken for a neurotic behaviour. Unconsciousness and grand mal convulsions may follow which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with normal respiration and loss of the airway. In severe cases apnoea may occur. Acidosis, hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anesthetics.

Recovery is due to redistribution and subsequent metabolism and excretion of the local anesthetic drug. Recovery may be rapid unless large amounts of the drug have been administered.

Cardiovascular system toxicity may be seen in severe cases and is generally preceded by signs of toxicity in the central nervous system. In patients under heavy sedation or receiving a general anesthetic, prodromal CNS symptoms may be absent. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anesthetics, but in rare cases cardiac arrest has occurred without prodromal CNS effects.

Cardiovascular toxic reactions are usually related to depression of the conduction system of the heart and myocardium, leading to decreased cardiac output, hypotension, heart block, bradycardia and sometimes ventricular arrhythmias, including ventricular tachycardia, ventricular fibrillation and cardiac arrest.

In children, early signs of local anesthetic toxicity may be difficult to detect in cases where the block is given during general anesthesia.

Treatment

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

THE FIRST STEP IN THE MANAGEMENT OF SYSTEMIC TOXIC REACTIONS, AS WELL AS UNDERVENTILATION OR APNEA, CONSISTS OF THE IMMEDIATE ESTABLISHMENT AND MAINTENANCE OF A PATENT AIRWAY AND ASSISTED OR CONTROLLED VENTILATION WITH 100% OXYGEN AND A DELIVERY SYSTEM CAPABLE OF PERMITTING IMMEDIATE POSITIVE AIRWAY PRESSURE BY MASK OR ENDOTRACHEAL INTUBATION. This may prevent convulsions if they have not already occurred.

Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (such as epinephrine or ephedrine which enhance myocardial contractility).

If necessary, use drugs to control convulsions. A bolus intravenous injection of a muscle relaxant (e.g., succinylcholine 1 mg/kg of body weight) will paralyze the patient without depressing the central nervous or cardiovascular systems and facilitate endotracheal intubation,

controlled ventilation, and secure optimal oxygenation. An anticonvulsant should be given intravenously if the convulsions do not stop spontaneously in 15-20 seconds. A bolus intravenous dose of diazepam (0.1 mg/kg) or thiopental (1-3 mg/kg) will permit ventilation and counteract central nervous system stimulation, but these drugs also depress central nervous system, respiratory, and cardiac function, add to possible depression, and may result in apnea. Thiopental will control convulsions rapidly, while the action of diazepam will be slower. Prolonged convulsions may jeopardize the patient's ventilation and oxygenation. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should only be administered by those familiar with their use. For specific techniques and procedures, refer to standard textbooks.

Recent clinical data from patients experiencing local anesthetic-induced convulsions demonstrated rapid development of hypoxia, hypercarbia and acidosis with bupivacaine within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

If cardiovascular depression is evident (hypotension, bradycardia), ephedrine 5-10 mg should be given intravenously and may be repeated, if necessary, after 2-3 minutes. Children should be given ephedrine doses commensurate with their age and weight.

Should circulatory arrest occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance, since hypoxia and acidosis will increase the systemic toxicity of local anesthetics. Epinephrine (0.1-0.2 mg intravenous or intracardial injections) should be given as soon as possible and repeated, if necessary. A successful resuscitation may require prolonged efforts.

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 foetal 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 should be accomplished. Resuscitation of obstetrical patients may take longer than resuscitation of nonpregnant patients and closed-chest cardiac compression may be ineffective. Rapid delivery of the foetus may improve the response to resuscitative efforts.

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Bupivacaine is a long-acting, amide-type local anesthetic with both anesthetic and analgesic effects. At high doses it produces surgical anesthesia, while at lower doses it produces sensory block (analgesia) with less pronounced motor block.

Mechanism of Action

Bupivacaine stabilizes the neuronal membrane and prevents both the generation and the conduction of nerve impulses, thereby exerting a local anesthetic action. As with other local anesthetics, bupivacaine causes a reversible blockade of impulse propagation along nerve fibers by preventing the inward movement of sodium ions through the cell membrane of the nerve fibers. The sodium channel of the nerve membrane is considered a receptor for local anesthetic molecules.

Onset and Duration of Action

The onset of action is rapid, and anesthesia is long lasting. The duration of action of a local anesthetic is dependent on a number of factors including site of injection, route of administration, concentration and volume (see **DOSAGE AND ADMINISTRATION**). It has also been noted that there is a period of analgesia that persists after the return of sensation, during which time the need for strong analgesics is reduced. The presence of epinephrine may prolong the duration of action for infiltration and peripheral nerve blocks but has less marked effect on epidural blocks.

MARCAINE 0.5% has a long duration of action of 2-5 hours following a single epidural injection and up to 12 hours after peripheral nerve blocks. The onset of blockade is slower than with lidocaine, especially when anesthetizing large nerves. When used in low concentrations, i.e., 0.25%, there is less effect on motor nerve fibers and the duration of action is shorter.

Hemodynamics

Bupivacaine, like other local anesthetics, may also have effects on other excitable membranes e.g. in the brain and myocardium. If excessive amounts of drug reach the systemic circulation rapidly, symptoms and signs of toxicity will appear, emanating mainly from the central nervous and cardiovascular systems.

Central nervous system toxicity (see **OVERDOSAGE**) usually precedes the cardiovascular effects as central nervous system toxicity occurs at lower plasma concentrations. Direct effects of local anesthetics on the heart include slow conduction, negative inotropism and eventually cardiac arrest.

Indirect cardiovascular effects (hypotension, bradycardia) may occur after epidural administration depending on the extent of the concomitant sympathetic block.

Pharmacokinetics

Absorption: The plasma concentration of local anesthetics is dependent upon the dose, the route of administration, the patient's hemodynamic/circulatory condition, and the vascularity of the injection site. The addition of epinephrine to bupivacaine may decrease the peak plasma concentration, whereas the time to peak plasma concentration usually is little affected. The effect varies with the type of block, dose and concentration.

Following injection of MARCAINE for caudal, epidural, or peripheral nerve block in man, peak levels of MARCAINE in the blood are reached in 30 to 45 minutes, followed by a gradual decline to insignificant levels during the next three to six hours. Intercostal blocks give the highest peak plasma concentration due to a rapid absorption (maximum plasma concentrations in the order of 1-4 mg/L after a 400 mg dose), while subcutaneous abdominal injections give the lowest plasma concentration. Epidural and major plexus blocks are intermediate. In children, rapid absorption and high plasma concentrations (in the order of 1-1.5 mg/L after a dose of 3 mg/kg) are seen with caudal block.

Bupivacaine shows complete, biphasic absorption from the epidural space with plasma half-lives in the order of seven minutes after initial administration, slowing to six hours over time. The slow absorption is rate-limiting in the elimination of bupivacaine, which explains why the apparent elimination half-life after epidural administration is longer than after intravenous administration.

Distribution: Local anesthetics are bound to plasma proteins in varying degrees. The highly lipophilic agents, such as bupivacaine, are far more highly protein-bound than the more hydrophilic compounds. Bupivacaine is approximately 95% protein-bound in normal adults. Generally, the lower the plasma concentration of drug, the higher the percentage of drug bound to plasma proteins. If plasma protein concentrations are decreased, more of the free drug will be available to exert activity. Bupivacaine is mainly bound to alpha-1-acid glycoprotein.

Bupivacaine readily crosses the placenta and equilibrium in regard to the unbound concentration is rapidly reached. 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. The degree of plasma protein binding in the foetus is less than in the mother, which results in lower total plasma concentrations in the foetus than in the mother. The free concentration, however, is the same in both mother and foetus.

Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding because only the free, unbound drug is available for placental transfer. MARCAINE with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4).

Bupivacaine has a total plasma clearance of 0.58 L/min a volume of distribution at steady state of 73 L.

An increase in total plasma concentration has been observed during continuous epidural infusion for postoperative pain relief. This is related to a postoperative increase in alpha-1-acid glycoprotein. The unbound, i.e. pharmacologically active, concentration is similar before and after surgery.

Metabolism: Because of its amide structure, bupivacaine is extensively metabolized in the liver predominantly by aromatic hydroxylation to 4-hydroxy-bupivacaine and N-dealkylation to 2,6-pipecoloxylidine (PPX), both mediated by cytochrome P450 3A4. The major metabolite of bupivacaine is pipecoloxylidine, a dealkylated derivative. Patients with hepatic disease may be more susceptible to the potential toxicities of the amide-type local anesthetics.

Excretion: The plasma elimination half-life of MARCAINE in adults is 2.7 hours (range 1.2 to 4.6 hours). In infants, the half-life ranges from 6 to 22 hours, thus it is significantly longer than in adults. Half-life is also prolonged in the elderly. Bupivacaine has an intermediate hepatic extraction ratio of 0.38 after intravenous administration. In children between 1 to 7 years the pharmacokinetics are similar to those in adults.

The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by renal perfusion and factors affecting urinary pH.

Clearance of bupivacaine is almost entirely due to liver metabolism and more sensitive to changes in intrinsic hepatic enzyme function than to liver perfusion.

STORAGE AND STABILITY

Store MARCAINE (bupivacaine hydrochloride), MARCAINE SPINAL (bupivacaine hydrochloride) and MARCAINE E (bupivacaine hydrochloride with epinephrine) at 20°C-25°C. Do not freeze. Protect MARCAINE E (bupivacaine hydrochloride with epinephrine) from light. Do not use if solution is coloured or contains a precipitate.

SPECIAL HANDLING INSTRUCTIONS

Adequate precautions should be taken to avoid prolonged contact between local anesthetic solutions containing epinephrine (low pH) and metal surfaces (e.g., needles or metal parts of syringes), since dissolved metal ions, particularly copper ions, may cause severe local irritation (swelling, oedema) at the site of injection and accelerate the degradation of epinephrine.

Isotonic Solutions

These solutions are not for spinal anesthesia.

Bupivacaine hydrochloride Solutions of **MARCAINE** that do not contain epinephrine may be autoclaved. Autoclave at 15-pound pressure, 121°C (250°F) for 15 minutes. Do not use if solution is discoloured or contains a precipitate.

BUPIVACAINE HYDROCHLORIDE WITH EPINEPHRINE 1:200,000 (as bitartrate)

Due to the heat sensitivity of epinephrine, solutions of MARCAINE E (which contain epinephrine) must not be autoclaved and should be protected from light. Do not use if solution is pinkish or darker than slightly yellow or contains a precipitate.

Adequate precautions should be taken to avoid prolonged contact between local anesthetic solutions containing epinephrine (low pH) and metal surfaces (e.g., needles or metal parts of syringes), since dissolved metal ions, particularly copper ions, may cause severe local irritation (swelling, oedema) at the site of injection and accelerate the degradation of epinephrine.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

The solubility of bupivacaine is limited at pH > 6.5. This must be taken into consideration when alkaline solutions, i.e., carbonates, are added since precipitation might occur. In the case of epinephrine-containing solutions, mixing with alkaline solutions may cause rapid degradation of epinephrine.

Composition and Packaging

Isotonic Solutions

- **0.25% - Contains 2.5 mg bupivacaine hydrochloride per mL**
  Single-dose vials of 10 mL (without preservative) box of 5
  Single-dose vials of 20 mL (without preservative) box of 5
  Multiple-dose vials of 50 mL (with methylparaben as preservative) box of 1

- **0.5% - Contains 5 mg bupivacaine hydrochloride per mL**
  Single-dose vials of 10 mL (without preservative) box of 5
  Single-dose vials of 20 mL (without preservative) box of 5
  Multiple-dose vials of 50 mL (with methylparaben as preservative) box of 1

- **0.75% - Contains 7.5 mg bupivacaine hydrochloride per mL**
  Single-dose vials of 20 mL (without preservative) box of 5

BUPIVACAINE HYDROCHLORIDE WITH EPINEPHRINE 1:200,000 (as bitartrate)

- **0.25% - with epinephrine 1:200,000**
  Contains 2.5 mg bupivacaine hydrochloride per mL
  Single-dose vials of 20 mL (without preservative) box of 5

- **0.5% - with epinephrine 1:200,000**
  Contains 5 mg bupivacaine hydrochloride per mL
  Single-dose vials of 20 mL (without preservative) box of 5

These solutions are made isotonic with sodium chloride and the pH is adjusted with sodium hydroxide or hydrochloric acid. The pH range for solutions without epinephrine is 4.0 to 6.5 and, for solutions with epinephrine, is 3.4 to 4.5. Each mL of solution with epinephrine contains 0.0091 mg epinephrine bitartrate and, as non-medicinal ingredients, 0.5 mg sodium metabisulfite, 1.25 mg monothioglycerol, and 2 mg ascorbic acid as antioxidants, 1.33 mg sodium lactate buffer and 0.1 mg edetate calcium disodium as stabilizer.

0.75% - hyperbaric solution for spinal use only

MARCAINE spinal solution is supplied in 2 mL single dose ampoules (boxes of 10) containing 0.75% hyperbaric solution.

Each mL of solution contains 7.5 mg bupivacaine hydrochloride and 82.5 mg dextrose in Water for Injection. The pH is adjusted between 4.0 and 6.5 with sodium hydroxide or hydrochloric acid. The solution may be autoclaved once at 15-pound pressure, 121°C (250°F) for 15 minutes. Do not administer any solution which is discoloured or contains particulate matter.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

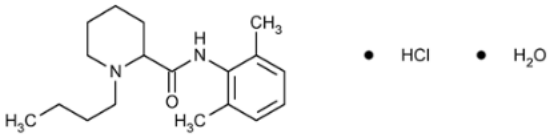
Bupivacaine Hydrochloride

Proper name: bupivacaine

Chemical name: 2-Piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-, monohydrochloride

Molecular formula and molecular mass: $C_{18}H_{28}N_2O \cdot HCl \cdot H_2O$ and 342.90

Structural formula:



Physicochemical properties: It is a white, crystalline powder that is freely soluble in 95 percent ethanol, soluble in water, and slightly soluble in chloroform or acetone.

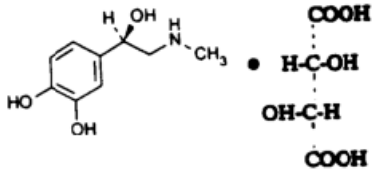
Epinepherine

Proper name: epinephrine bitartrate

Chemical name: 1,2-benzenediol,4-[1-hydroxy-2-(methylamino)ethyl]-, (R)-,[R- (R*,R*)]-2,3-dihydroxybutanedioate(1:1) salt

Molecular Formula and Molecular Mass: $C_9H_{13}NO_3 \bullet C_4H_6O_6$ and 333.29

Structural Formula:



Physicochemical Properties: White or greyish white or light brownish grey, odourless crystalline powder, which slowly darkens on exposure to light. Freely soluble in water. Slightly soluble in alcohol. Practically insoluble in chloroform and in ether. Solutions are acidic, with pH approximately 3.5.

DETAILED PHARMACOLOGY

Local anesthetics block 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.

After injection of bupivacaine for caudal, epidural or peripheral nerve block in man, peak blood levels were reached in 30 to 45 minutes, followed by a decline to insignificant levels in the next 3 to 6 hours.

In metabolic studies in the rat, subcutaneous doses of C^{14} - labelled bupivacaine were rapidly absorbed. The gastrointestinal tract, liver, spleen and kidney showed relatively high concentrations. Radioactivity in adipose tissue was high immediately after drug administration but decreased rapidly and was not detected at 24 hours.

The principal route of biotransformation in the rat is by conjugation with glucuronic acid. Because of its amide structure, bupivacaine is not detoxified by plasma esterases.

As for other local anesthetics, bupivacaine is metabolized in the liver predominantly by aromatic hydroxylation to 4-hydroxy-bupivacaine and N-dealkylation to 2,6-pipecoloxylidine (PPX), both mediated by cytochrome P450 3A4. The metabolites have a pharmacological activity that is less than that of bupivacaine. Bupivacaine and the metabolites are excreted mainly via the kidneys.

TOXICOLOGY

Acute LD_{50} determinations in the mouse and rat were as follows:

	Route of Administration	**Species**	**Acute LD_{50} ±s.e. mg/kg at 24 hours**
Bupivacaine hydrochloride 0.5%	I.V. I.V. S.C. S.C.	Mouse Rat Mouse Rat	7.1 ± 0.6 6.2 ± 0.5 63 ± 7 63 ± 9
Bupivacaine hydrochloride 0.5% with epinephrine 1:200,000	I.V. I.V. S.C. S.C.	Mouse Rat Mouse Rat	6.5 ± 0.4 5.4 ± 0.4 66 ± 8 51 ± 8
Bupivacaine hydrochloride 0.75% (Hyperbaric)	I.V.	Mouse	6.2 ± 0.4

I.V.: Intravenous
S.C.: Subcutaneous

At high intravenous doses in mice and rats, symptoms of toxicity included CNS stimulation followed by convulsions. Central stimulation is followed by depression and death is usually due to respiratory depression. Dogs tolerated single intramuscular doses of up to 10 mg/kg, with and without epinephrine.

Bupivacaine produced seizures in rhesus monkeys when serum levels reached the 4.5 to 5.5 µg/mL range.

No significant pathologic changes were observed following sub-lethal doses of bupivacaine in the rat, rabbit, dog and monkey, except for dose-related inflammatory reactions in the muscle tissue at the injection sites. In irritation studies in the rabbit, healing of the intramuscular lesions was well advanced or complete within seven days after the injection.

Libelius and others reported denervation-like changes in the skeletal muscle of rats following repeated intramuscular injection into the same site. They commented, however, that the conditions under which these changes occurred are not likely to be encountered in the clinical use of the drug.

No immediate or delayed allergic responses were observed in the guinea pig after sensitivity testing. No evidence of drug-induced teratogenic effects was observed in rats and rabbits given subcutaneous injections of bupivacaine.

Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine hydrochloride was administered to these species in doses comparable to nine and five times, respectively the maximal recommended daily human dose (400 mg).

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PART III: CONSUMER INFORMATION

MARCAINE®
(Bupivacaine Hydrochloride Injection USP)

MARCAINE® SPINAL
(Bupivacaine Hydrochloride in Dextrose Injection USP)

MARCAINE® E
(Bupivacaine Hydrochloride and Epinephrine Injection USP)

This leaflet is part III of a three-part "Product Monograph" published when Marcaine, Marcaine Spinal and Marcaine E were approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Marcaine, Marcaine Spinal and Marcaine E. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
MARCAINE, MARCAINE SPINAL and MARCAINE E are used to anesthetize part of the body for surgical operations and also for pain relief, and can be used:
- to anesthetize the area of the body where surgery is to be performed;
- to provide pain relief in labour and after surgery or acute injury.

What it does:
MARCAINE, MARCAINE SPINAL and MARCAINE E act by temporarily preventing the nerves in the injected area from transmitting sensations of pain, heat or cold. However, you may still experience sensations such as pressure and touch. In this way the nerve(s) is anesthetized/ numbed in the part of the body, which will be subjected to surgery. In many cases this means that the nerves to the muscles in the area will also be blocked, causing temporary weakness or paralysis.

When it should not be used:
MARCAINE, MARCAINE SPINAL and MARCAINE E should not be used in patients who are allergic to:
- bupivacaine hydrochloride
- any other "-caine" type anesthetics
- any of the non-medicinal ingredients in the product (see **What the non-medicinal ingredients are** below)

MARCAINE (multidose vials) should not be used in patients who are allergic to methylparaben, other parabens or PABA.

MARCAINE E should not be used in patients who are allergic to:
- sodium metabisulfite

Because of the potential for irreversible joint damage, pain following joint surgery should not be managed by infusing MARCAINE, MARCAINE SPINAL and MARCAINE E into the joint (i.e. by use of a post-operative "pain pump").

What the medicinal ingredients are:
Bupivacaine hydrochloride.
Bupivacaine hydrochloride with epinephrine.

What the non-medicinal ingredients are:
MARCAINE contains sodium chloride, sodium hydroxide and/or hydrochloric acid and water for injection. Multidose vials contain methylparaben as a preservative.

MARCAINE E contains sodium chloride, sodium hydroxide and/or hydrochloric acid, monothioglycerol, ascorbic acid, sodium lactate 60% solution, edetate calcium disodium, sodium metabisulfite and water for injection.

MARCAINE SPINAL contains dextrose, sodium hydroxide and/or hydrochloride acid and water for injection.

What dosage forms it comes in:
MARCAINE is available as 0.25% (2.5 mg/mL), 0.5% (5 mg/mL) and 0.75% (7.5 mg/mL) in single-dose glass vials of 10 and 20 mL as well as multidose vials of 50 mL.

MARCAINE E is available in single-dose glass vials as 0.25% (2.5 mg/mL) and 0.5% (5 mg/mL) with epinephrine (as bitartrate) (1:200,000).

MARCAINE SPINAL is available in single-dose glass vials as 0.75% (7.5 mg/mL).

WARNINGS AND PRECAUTIONS

You should talk to your doctor prior to surgery:
- about health problems you have now or have had in the past;
- about other medicines you take, including ones you can buy without prescription;
- if you are taking other medicines such as drugs used to treat irregular heart activity (anti-arrhythmics);
- if you have ever had a bad, unusual allergic reaction to bupivacaine or any other medicines ending with "-caine";
- if you are allergic to methylparaben, other parabens or PABA;
- if you think you may be allergic or sensitive to any ingredients in MARCAINE, MARCAINE E or MARCAINE SPINAL (see above). Sodium metabisulphite might cause allergic reactions (e.g., itching, hives, facial swelling and breathing difficulties) in susceptible people, especially those with a history of asthma or allergy;
- if you have heart, liver or kidney disease;
- if you are pregnant, plan to become pregnant or are breastfeeding;
- if you are planning to drive or operate any tools or machinery on the day of surgery, because MARCAINE, MARCAINE E and MARCAINE SPINAL may temporarily interfere with your reactions and muscular coordination.

INTERACTIONS WITH THIS MEDICATION

Many drugs interact with MARCAINE, MARCAINE E and MARCAINE SPINAL. Tell your doctor about all prescription, over-the-counter and natural health products that you are using (See WARNINGS AND PRECAUTIONS above).

Usage of such medicines at the same time as MARCAINE, MARCAINE E or MARCAINE SPINAL may increase the risk of serious side effects.

PROPER USE OF THIS MEDICATION

Usual dose:
MARCAINE, MARCAINE E and MARCAINE SPINAL should be administered by a doctor. The dose given is decided by the doctor based on the clinical need and your physical condition.

Overdose:
Serious adverse effects resulting from an overdose are extremely rare and need special treatment. The doctor is trained and equipped to handle such situations.

The first signs that too much MARCAINE, MARCAINE E or MARCAINE SPINAL has been given usually take the form of lightheadedness, numbness of the lips and round the mouth, numbness of the tongue, hearing disturbances, tingling in the ears, and visual disturbances. Tell your doctor immediately if you notice any of these symptoms. Speech symptoms, muscular twitching or tremors are more serious.

In the event of serious overdose or a misplaced injection, trembling, seizures or unconsciousness may occur.

If the administration of MARCAINE, MARCAINE E and MARCAINE SPINAL is stopped as soon as early signs of overdose appear, the risk of serious adverse effects rapidly decreases.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like any medication, MARCAINE, MARCAINE E and MARCAINE SPINAL may cause side effects in some people.

Medicines affect different people in different ways. Just because side effects have occurred in some patients, does not mean that you will get them.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Sudden life-threatening allergic reactions (such as anaphylaxis) are rare, affecting less than 1 in 1,000 people. Possible symptoms include sudden onset of rash, itching or lumpy rash (hives); swelling of the face, lips, tongue or other parts of the body; and shortness of breath, wheezing or difficulty breathing. **If you think that MARCAINE, MARCAINE E or MARCAINE SPINAL is causing an allergic reaction, tell your doctor immediately.**

There are other possible side effects that have been reported for MARCAINE, MARCAINE E and MARCAINE SPINAL. Tell your doctor or anesthesia professional if you experience any of the following side effects:

Frequency	Symptom/ Effect
Very Common	**Low blood pressure (hypotension). This might make you feel dizzy or light-headed.**
	Feeling sick (nausea).
Common	**Pins and needles.**
	Feeling dizzy.
	Headache.
	Slow or fast heart beat (bradycardia, tachycardia).
	High blood pressure (hypertension).
	Being sick (vomiting).
	Difficulty in passing urine.
	High temperature (fever) or stiffness (rigor).
	Back pain.
Uncommon	**Anxiety.**
	Decreased sensitivity or feeling in the skin.
	Fainting.
	Difficulty breathing.
	Low body temperature (hypothermia).
	Some symptoms can happen if the injection was given into a blood vessel by mistake, or if you have been given too much MARCAINE, MARCAINE E or MARCAINE SPINAL (see also "OVERDOSE" section above). These include fits (seizures), feeling dizzy or light-headed, numbness of the lips and around the mouth, numbness of the tongue, hearing problems, problems with your sight (vision), problems with your speech, stiff muscles, and trembling.
Rare	**Heart attack (cardiac arrest).**
	Uneven heart beat (arrhythmias).

Other possible side effects include:

Numbness, due to nerve irritation caused by the needle or the injection. This does not usually last for long.

Possible side effects seen with other local anesthetics which might also be caused by MARCAINE, MARCAINE E or MARCAINE SPINAL include:

Damaged nerves. Rarely (affecting less than 1 in 1,000 people), this may cause permanent problems.

If too much MARCAINE, MARCAINE E or MARCAINE SPINAL is given into the spinal fluid, the whole body may become numbed (anesthetised).

This is not a complete list of side effects. For any unexpected effects while taking MARCAINE, MARCAINE SPINAL or MARCAINE E, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

NOTE: This CONSUMER INFORMATION leaflet provides you with the most current information at the time of printing.

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Pfizer Canada ULC, at: 1-800-463-6001.

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