PRODUCT MONOGRAPH

Bupivacaine Hydrochloride in Dextrose Injection USP

7.5 mg bupivacaine hydrochloride / mL

Sterile Hyperbaric Solution

Local Anesthetic for Spinal Use Only

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Date of Preparation:
March 27, 2023

Control No.: 263877

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Bupivacaine Hydrochloride in Dextrose Injection USP
0.75%

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Spinal	Bupivacaine Hydrochloride in Dextrose Injection USP Sterile Solution 0.75% hyperbaric solution	Dextrose, sodium hydroxide and/or hydrochloric acid and water for injection.

INDICATIONS AND CLINICAL USE

Adults (> 18 years of age):

Bupivacaine Hydrochloride in Dextrose Injection USP is indicated for the production of local or regional anaesthesia and analgesia with the following procedure:

- Subarachnoid (spinal) blocks

Standard procedures for subarachnoid (spinal) blocks 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

Bupivacaine Hydrochloride in Dextrose Injection USP is contraindicated:

- In patients with a hypersensitivity to bupivacaine, or to any local anaesthetic agent of the amide type, or to other components of bupivacaine injection.
- In severe shock and in heart block and when there is inflammation and/or sepsis near the site of the proposed injection.

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 ANAESTHETICS 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.

AN INTRAVENOUS CANNULA MUST BE INSERTED BEFORE THE LOCAL ANAESTHETIC 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 ANAESTHETIC THAT RESULTS IN EFFECTIVE ANAESTHESIA 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.

Cardiovascular

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

Subarachnoid (spinal) blocks 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 i.m. 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.

Local anaesthetics 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 anaesthetics.

Patients with partial or complete heart block require special attention since local anaesthetics 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.

Subarachnoid (spinal) anaesthesia should be used with caution in patients with impaired cardiovascular function.

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.

Hepatic

Because amide-type local anaesthetics 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 anaesthetics 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,** and **ADVERSE REACTIONS** and **OVERDOSAGE**). During major regional nerve blocks, the patients should be in an optimal condition and have i.v. 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 anaesthetic 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 anaesthetics should be used with caution in patients in poor general condition due to severe renal dysfunction although regional anaesthesia is frequently indicated in these patients.

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 anaesthesia or analgesia.

Labour and Delivery: The 0.75% hyperbaric solution of Bupivacaine Hydrochloride in Dextrose Injection USP should be used for women during Labour and Delivery only if the potential benefit justifies the potential risk to the mother and foetus.

Maternal hypotension has resulted from regional anaesthesia (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular**). Local anaesthetics 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.

Subarachnoid anaesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Subarachnoid anaesthesia may prolong the second stage of labour by removing the parturient's urge to bear down or by interfering with motor function. Obstetrical anaesthesia may increase the need for forceps assistance.

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.

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, Bupivacaine Hydrochloride in Dextrose Injection USP (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 anaesthetics 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 anaesthesia). 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 anaesthesia.

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 under ventilation 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 anaesthesia may occur. This may lead to secondary cardiac arrest if untreated.

Central Nervous System: 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** sections).

Allergic: Allergic type reactions are rare (<0.1%) and may occur as a result of sensitivity to local anaesthetics of the amide type. These reactions are characterized by signs such as urticaria, pruritus, 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 anaesthetic 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 anaesthesia. Neurological effects may be related to local anaesthetic 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 loss of 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 preoperative medication.

DRUG INTERACTIONS

Drug-Drug Interactions

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

Local anaesthetics

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 anaesthetics such as lidocaine, ropivacaine, mepivicaine 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.

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 or 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.

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 anaesthetic agents, like sedatives, are central nervous system depressants which in combination may have an additive effect.

General Anaesthetics- 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 anaesthesia 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 anaesthetics, 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 anaesthetics 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.

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 anaesthetic solution should be avoided and fractional doses should be used when feasible. In general, complete block of all nerve fibres 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 anaesthesia.

There have been adverse event reports of irreversible chondrolysis in patients receiving intraarticular infusions of local anesthetics following arthroscopic and other surgical procedures. Bupivacaine Hydrochloride in Dextrose Injection USP is not approved for this use (see **WARNINGS AND PRECAUTIONS**, General).

Special Populations

Local anaesthetics 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 anaesthesia 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. 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.

The 0.75% hyperbaric solution of Bupivacaine Hydrochloride in Dextrose Injection USP is recommended at term for obstetrical anesthesia and analgesia.

To avoid intravascular injection, aspiration should be repeated prior to and during administration of the main dose, which should be injected slowly, while closely observing the patient's vital functions and maintaining verbal contact.

Adults:

Dosage and administration of Bupivacaine Hydrochloride in Dextrose Injection USP should be managed according to the patient condition and standard of anaesthetic care. **See Spinal Use.**

Children:

Until further experience is gained, bupivacaine is not recommended for children younger than two years of age. The following restriction applies to the use of Bupivacaine Hydrochloride in Dextrose Injection USP for children over two years of age: Bupivacaine Hydrochloride in Dextrose Injection USP is not recommended for spinal use in patients younger than 18 years.

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 Hydrochloride in Dextrose Injection USP (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 Hydrochloride in Dextrose Injection USP (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

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 anaesthetics 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 anaesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively.

Symptoms

Accidental intravascular injections of local anaesthetics 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 anaesthetic 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 anaesthetics.

Recovery is due to redistribution and subsequent metabolism and excretion of the local anaesthetic 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 anaesthetic, prodromal CNS symptoms may be absent. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics, 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 anaesthetic toxicity may be difficult to detect in cases where the block is given during general anaesthesia.

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 anaesthetic 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 i.v. injection of a muscle relaxant (e.g., succinylcholine 1 mg/kg *bw*) 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 i.v. if the convulsions do not stop spontaneously in 15-20 seconds. A bolus i.v. 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 i.v. should be given 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 anaesthetics. 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 anaesthetic with both anaesthetic and analgesic effects. At high doses it produces surgical anaesthesia, 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 anaesthetics, bupivacaine causes a reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the cell membrane of the nerve fibres. The sodium channel of the nerve membrane is considered a receptor for local anaesthetic 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.

Hemodynamics

Bupivacaine, like other local anaesthetics, 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 anaesthetics 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 anaesthetics 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 bupivacaine for caudal, epidural, or peripheral nerve block in man, peak levels of bupivacaine 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. Bupivacaine 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 bupivacaine 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 i.v. 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 Bupivacaine Hydrochloride in Dextrose Injection USP at 15-30°C.

SPECIAL HANDLING INSTRUCTIONS

Bupivacaine Hydrochloride in Dextrose Injection USP may be autoclaved. Autoclave at 15-pound pressure, 121°C (250°F) for 15 minutes. Do not use product if solution shows haziness, particulate matter, discolouration, or leakage.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

Bupivacaine Hydrochloride in Dextrose Injection USP is a sterile solution.

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.

Composition and Packaging

0.75% - hyperbaric solution for spinal use only

Bupivacaine Hydrochloride in Dextrose Injection USP spinal solution is supplied in 2 mL fill volume, single dose, preservative free ampoules containing 0.75% hyperbaric solution and is packaged into cartons containing 10 ampules each.

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Bupivacaine Hydrochloride

Proper Name:

Bupivacaine

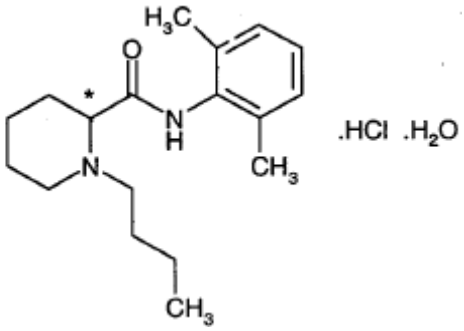
Chemical Name:

2-Piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl), monohydrochloride, monohydrate, (±)

Molecular formula and molecular mass:

$C_{18}H_{28}N_2O \cdot HCl \cdot H_2O$ 342.9 g/mol

Structural Formula:



Physiochemical Properties:

White crystalline powder that is soluble in water, freely soluble in ethanol and slightly soluble in chloroform and acetone. Slightly hygroscopic with a melting point of 258.5°C.

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 C14 - 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 anaesthetics, 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 HCl 0.75% (Hyperbaric)	I.V.	Mouse	6.2 ± 0.4

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.

Bupivacaine produced seizures in rhesus monkeys when serum levels reached the 4.5 to 5.5 mcg/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

Bupivacaine Hydrochloride in Dextrose Injection USP

0.75%

This leaflet is part III of a three-part "Product Monograph" published when Bupivacaine Hydrochloride in Dextrose Injection USP was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Bupivacaine Hydrochloride in Dextrose Injection USP. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Bupivacaine Hydrochloride in Dextrose Injection USP is used to anesthetize part of the lower body for pain relief or in surgical operations.

What it does:
Bupivacaine Hydrochloride in Dextrose Injection USP acts 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:
Bupivacaine Hydrochloride in Dextrose Injection USP should not be used in patients who are allergic to:

- bupivacaine hydrochloride
- any other "-caine" type anaesthetics
- any of the non-medicinal ingredients in the product (see WHAT THE NON-MEDICINAL INGREDIENT ARE below)

Bupivacaine Hydrochloride in Dextrose Injection USP should not be used;

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

What the medicinal ingredients are:
Bupivacaine hydrochloride.

What the non-medicinal ingredients are:
Bupivacaine Hydrochloride in Dextrose Injection USP contains dextrose anhydrous, sodium hydroxide and/or hydrochloride acid and water for injection.

What dosage forms it comes in:
Bupivacaine Hydrochloride in Dextrose Injection USP is a sterile solution available in single-dose glass ampoules 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 think you may be allergic or sensitive to any ingredients in Bupivacaine Hydrochloride in Dextrose Injection USP (see above).
- 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 Bupivacaine Hydrochloride in Dextrose Injection USP may temporarily interfere with your reactions and muscular coordination.

INTERACTIONS WITH THIS MEDICATION

Many drugs interact with Bupivacaine Hydrochloride in Dextrose Injection USP. 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 Bupivacaine Hydrochloride in Dextrose Injection USP may increase the risk of serious side effects.

PROPER USE OF THIS MEDICATION

Usual dose:
Bupivacaine Hydrochloride in Dextrose Injection USP should be administered by a doctor. The dose given is decided by the doctor based on the clinical need and your physical condition.

Overdose:

If you think you, or a person you are caring for, have taken too much Bupivacaine Hydrochloride in Dextrose Injection USP, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

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 Bupivacaine Hydrochloride in Dextrose Injection USP 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 Bupivacaine Hydrochloride in Dextrose Injection USP 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, Bupivacaine Hydrochloride in Dextrose Injection USP 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 Bupivacaine Hydrochloride in Dextrose Injection USP is causing an allergic reaction, tell your doctor immediately.**

There are other possible side effects that have been reported for Bupivacaine Hydrochloride in Dextrose Injection USP. 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 Bupivacaine Hydrochloride in Dextrose Injection USP (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 Bupivacaine Hydrochloride in Dextrose Injection USP include:
Damaged nerves. Rarely (affecting less than 1 in 1,000 people), this may cause permanent problems.

If too much Bupivacaine Hydrochloride in Dextrose Injection USP 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 Bupivacaine Hydrochloride in Dextrose Injection USP, 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

If you want more information about Bupivacaine Hydrochloride in Dextrose Injection USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.formativepharma.com or by calling 1-855-808-9528

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Last revised: March 27, 2023