

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

BUPIVACAINE HYDROCHLORIDE INJECTION, USP

Sterile Solution, 2.5 mg/mL, 5 mg/mL and 7.5 mg/mL,
Parenteral – Retrobulbar, Epidural, Block/Infiltration

USP

Local Anesthetic

Baxter Corporation
7125 Mississauga Rd,
Mississauga, Ontario L5N 0C2

Date of Initial Authorization:
May 23, 2019

Date of Revision:
December 6, 2023

Submission Control Number: 278636

RECENT MAJOR LABEL CHANGES

3 SERIOUS WARNINGS AND PRECAUTIONS BOX	12/2023
7 WARNINGS AND PRECAUTIONS, General, Hepatic/Biliary/Pancreatic	12/2023

TABLE OF CONTENTS

Sections or subsections that are no applicable at the time of authorization are not listed.

RECENT MAJOR LABEL CHANGES	2
TABLE OF CONTENTS	2
PART I: HEALTH PROFESSIONAL INFORMATION	4
1 INDICATIONS	4
1.1 Pediatrics.....	4
1.2 Geriatrics	4
2 CONTRAINDICATIONS	4
3 SERIOUS WARNINGS AND PRECAUTIONS BOX	5
4 DOSAGE AND ADMINISTRATION	6
4.1 Dosing Considerations	6
4.2 Recommended Dose and Dosage Adjustment	6
4.3 Reconstitution	7
4.4 Administration.....	7
5 OVERDOSAGE	10
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	12
7 WARNINGS AND PRECAUTIONS	13
7.1 Special Populations.....	18
7.1.1 Pregnant Women	18
7.1.2 Breast-feeding	19
7.1.3 Pediatrics	19
7.1.4 Geriatrics	19
8 ADVERSE REACTIONS	19

8.1	Adverse Reaction Overview.....	19
9	DRUG INTERACTIONS	22
9.4	Drug-Drug Interactions.....	22
9.5	Drug-Food Interactions.....	23
9.6	Drug-Herb Interactions.....	23
9.7	Drug-Laboratory Test Interactions.....	24
10	CLINICAL PHARMACOLOGY	24
10.1	Mechanism of Action.....	24
10.2	Pharmacodynamics	24
10.3	Pharmacokinetics	25
11	STORAGE, STABILITY AND DISPOSAL	27
12	SPECIAL HANDLING INSTRUCTIONS	27
13	PHARMACEUTICAL INFORMATION	28
14	CLINICAL TRIALS	28
15	MICROBIOLOGY	28
16	NON-CLINICAL TOXICOLOGY	28
17	SUPPORTING PRODUCT MONOGRAPHS	29
	PATIENT MEDICATION INFORMATION.....	30

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Adults (> 18 years of age):

Bupivacaine Hydrochloride Injection, USP (bupivacaine hydrochloride) is 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 blocks

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

1.1 Pediatrics

Pediatrics (< 2 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for use in children younger than two years. See also 4.4 Administration.

Until further experience is gained, the following restrictions apply to the use of Bupivacaine Hydrochloride Injection, USP: (a) isotonic bupivacaine solutions are not recommended for spinal use; (b) the 0.75% isotonic solution of bupivacaine is not recommended in patients younger than 12 years.

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See [7.1.4 Geriatrics](#).

2 CONTRAINDICATIONS

Bupivacaine Hydrochloride Injection, USP is contraindicated:

- In patients who are hypersensitive to bupivacaine, or any local anesthetic agent of the amide type, or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- 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 [4 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.
- Bupivacaine Hydrochloride Injection, USP 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.

Bupivacaine Hydrochloride Injection, USP 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.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

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 [8 ADVERSE REACTIONS](#) and [5 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 Bupivacaine Hydrochloride Injection, USP 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.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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.

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 0.50% 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. Bupivacaine Hydrochloride Injection, USP is not approved for this use (see [7 WARNINGS AND PRECAUTIONS, General](#)).

4.2 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 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 Bupivacaine Hydrochloride Injection, USP is not recommended for obstetrical anesthesia or analgesia (see [7 WARNINGS AND PRECAUTIONS](#)). The 0.5% and 0.25% concentrations of isotonic Bupivacaine Hydrochloride Injection, USP 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.

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.

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.

4.3 Reconstitution

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.

4.4 Administration

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	up to 60 ^b	up to 150 ^b	1-3	3-4	Surgical operations and postoperative analgesia.
	0.5	up to 30 ^b	up to 150 ^b	1-3	4-8	
Lumbar epidural	0.25	6-15	15-37.5	2-5	1-2	Labour and postoperative pain relief. Surgical operations including Caesarean Section.
	0.5	15-30	75-150	15-30	2-3	
Thoracic epidural	0.25	5-15	12.5-37.5	10-15	1.5-2	Surgical operation.
	0.5	5-10	25-50	10-15	2-3	
Caudal epidural	0.25	20-30	50-75	20-30	1-2	Pain relief and diagnostic use. Surgical operations and postoperative analgesia.
	0.5	20-30	100-150	15-30	2-3	
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 ^c	0.25	1-5	2.5-12.5	2-5	3-4	Surgical operations.
Peripheral nerves	0.25	up to 40 ^b	up to 100 ^b	10-20	3-5	Therapeutic (pain relief).
	0.5	up to 30 ^b	up to 150 ^b	5-10	4-8	Surgical operations.
Sympathetic ^d Stellate block	0.25	5-15	12.5-37.5	10-20	3-6	Ischemic conditions or sympathetic maintained pains <i>e.g.</i> , visceral pain conditions such as pancreatitis or cancer, pain of herpes zoster.
Lumbar Paravertebral block	0.25	10-20	25-50	10-20	3-6	
Coeliac plexus block	0.25	20-40	50-100	10-20	3-6	

- ^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. Bupivacaine Hydrochloride Injection, USP is not approved for this use (see [7 WARNINGS AND PRECAUTIONS, General](#)).
- ^c Without epinephrine.
- ^d See [7 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 Bupivacaine Hydrochloride Injection, USP for children over two years of age: (a) isotonic bupivacaine solutions are not recommended for spinal use; (b) the 0.75% isotonic solution of bupivacaine is not recommended in patients younger than 12 years.

For bolus administration or intermittent injections, unless stated otherwise (see Table 2), a dose of up to 2 mg/kg of bupivacaine 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. For the appropriate suggested concentrations and dosage, see the following table:

Table 2 Dosage recommendations in children (over two years of age) for bupivacaine 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 ^b			
-Lumbosacral	0.25	0.5	1.25 ^c
-Thoracolumbar	0.25	0.6- 1.0	1.5- 2.5 ^c
Lumbar epidural	0.25	0.5-1.0	1.25- 2.5
	0.5	0.3-0.5	1.5-2.5
Dorsal (penile)	0.25 ^a	0.1-0.2	0.25-0.5
	0.5 ^a	0.1-0.2	0.5-1.0

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

^a Without epinephrine

^b Consider both age and weight for calculation of dosages

^c 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 [7 WARNINGS AND PRECAUTIONS](#)). 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 [2 CONTRAINDICATIONS](#)).

5 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 [8 ADVERSE REACTIONS](#) and [7 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, hyperacusis, 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Parenteral - Retrobulbar, Epidural, Block/Infiltration	Bupivacaine Hydrochloride Injection USP 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.

Composition

Bupivacaine Hydrochloride Injection, USP, 2.5 mg/mL - preservative free

- **Each mL contains:** Bupivacaine hydrochloride USP 2.5 mg.
- Non-medicinal ingredients: 8.6 mg of Sodium Chloride, sufficient quantity of Sodium Hydroxide and/or Hydrochloric Acid added to adjust pH and Water for Injection.

Bupivacaine Hydrochloride Injection, USP, 5 mg/mL – with preservative

- **Each mL contains:** Bupivacaine hydrochloride USP 5 mg.
Non-medicinal ingredients: 1 mg of Methylparaben (as preservative), 8.1 mg of Sodium Chloride, Sufficient quantity of Sodium Hydroxide and/or Hydrochloric Acid added to adjust pH and Water for Injection.

Bupivacaine Hydrochloride Injection, USP, 7.5 mg/mL - preservative free

- **Each mL contains:** Bupivacaine hydrochloride USP 7.5 mg.
Non-medicinal ingredients: 7.6 mg of Sodium Chloride, sufficient quantity of Sodium Hydroxide and/or Hydrochloric Acid added to adjust pH and Water for Injection.

Packaging

Bupivacaine Hydrochloride Injection, USP, 2.5 mg/mL

Single-dose vials of 10 mL (without preservative) box of 10

Single-dose vials of 20 mL (without preservative) box of 10

Single- dose vials of 30 mL (without preservative) box of 1

Bupivacaine Hydrochloride Injection, USP, 5 mg/mL

Multiple-dose vials of 50 mL (with methylparaben as preservative) box of 1

Bupivacaine Hydrochloride Injection, USP, 7.5 mg/mL

Single- dose vials of 10 mL (without preservative) box of 10

Single-dose vials of 20 mL (without preservative) box of 10

Single-dose vials of 30 mL (without preservative) box of 1

7 WARNINGS AND PRECAUTIONS

General

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 intra-articular 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. **Bupivacaine Hydrochloride Injection, USP should not be used for postoperative intra-articular infusion** (see [4 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.

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.

Hypersensitivity

Bupivacaine Hydrochloride Injection, USP 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 [2 CONTRAINDICATIONS](#)).

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.

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.

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Ear/Nose/Throat

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 [4 DOSAGE AND ADMINISTRATION](#)).

Hepatic/Biliary/Pancreatic

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.

Drug Induced Liver Injury (DILI): Serious cases of drug-induced liver injury (DILI), hepatic failure, and increased hepatic enzymes have been reported with bupivacaine, especially following repeated injections or long-term infusions. These events were not dose dependent, and patients were adults of all ages, with or without previous history of hepatic-related events. Stop administration of bupivacaine if signs of hepatic dysfunction are observed during treatment. Re-challenge should be avoided (see [8 ADVERSE REACTIONS](#)).

Ophthalmologic

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 [7 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 conjunctiva.

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.

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 [7 WARNINGS AND PRECAUTIONS](#), [8 ADVERSE REACTIONS](#) and [5 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 [4 DOSAGE AND ADMINISTRATION](#)), and should be familiar with the diagnosis and treatment of side effects, systemic toxicity and other complications (see [8 ADVERSE REACTIONS](#) and [5 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.

Reproductive Health: Female and Male Potential

See [2 CONTRAINDICATIONS](#), [7.1.1 Pregnant Women](#).

- **Fertility**

No data are available.

- **Teratogenic Risk**

Please see [16 NON-CLINICAL TOXICOLOGY](#).

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

7.1.1 Pregnant Women

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 [7 WARNINGS AND PRECAUTIONS](#)). This, however, does not exclude the use of isotonic Bupivacaine Hydrochloride Injection, USP 0.25% or 0.5% at term for obstetrical anesthesia or analgesia.

Bupivacaine is contraindicated for obstetrical paracervical block anesthesia (see [7 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 [7 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 bupivacaine hydrochloride 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.

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

Pediatrics (< 2 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for use in children younger than two years.

Until further experience is gained, the following restrictions apply to the use of Bupivacaine Hydrochloride Injection, USP: (a) isotonic bupivacaine solutions are not recommended for spinal use; (b) the 0.75% isotonic solution of bupivacaine is not recommended in patients younger than 12 years.

7.1.4 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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 [5 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, hyperacusis, 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 [7 WARNINGS AND PRECAUTIONS, Cardiovascular](#) and [5 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.

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 paralyzes (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.

Cauda equina and lumbosacral cord complications (usually consisting of arachnoiditis and demyelination) 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.

Hepatobiliary system

Drug induced liver injury (DILI), hepatic failure, jaundice and other signs of hepatic dysfunction (increased alanine aminotransferase (ALT), alkaline phosphates (AlkP) and bilirubin) have been observed following bupivacaine use (see [7 WARNINGS AND PRECAUTIONS](#)).

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

See [7 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 effects 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.

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.

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.

H₂-antagonists

The H₂-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 H₂ blockers prior to epidural anesthesia is inadvisable since toxic levels of local anesthetic may result.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 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.

10.1 Mechanism of Action

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.

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.

10.2 Pharmacodynamics

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 [4 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.

Bupivacaine Hydrochloride Injection, USP 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.

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 [5 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.

10.3 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 Bupivacaine Hydrochloride Injection, USP for caudal, epidural, or peripheral nerve block in man, peak levels of Bupivacaine Hydrochloride Injection, USP 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 Hydrochloride Injection, USP 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-pipecoloxylidene (PPX), both mediated by cytochrome P450 3A4. The major metabolite of bupivacaine is pipecoloxylidene, a dealkylated derivative. Patients with hepatic disease may be more susceptible to the potential toxicities of the amide-type local anesthetics.

Elimination

The plasma elimination half-life of Bupivacaine Hydrochloride Injection, USP 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.

Special Populations and Conditions

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

11 STORAGE, STABILITY AND DISPOSAL

Store at 15°C-30°C. Discard any unused portion. Do not freeze. Do not use product if solution shows haziness, particulate matter, discoloration, or leakage.

12 SPECIAL HANDLING INSTRUCTIONS

Isotonic Solutions

These solutions are not for spinal anesthesia.

Bupivacaine hydrochloride solutions 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 discolored or contains a precipitate.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

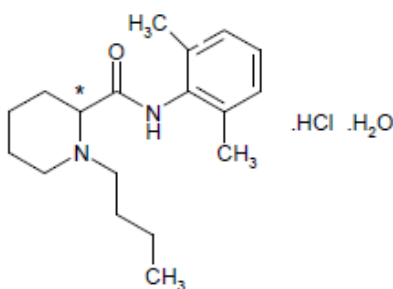
Drug Substance

Proper name: Bupivacaine hydrochloride

Chemical name: (2RS)-1-Butyl-N-(2,6-dimethylphenyl) piperidine-2-carboxamide hydrochloride monohydrate

Molecular formula and molecular mass: $C_{18}H_{28}N_2O \cdot HCl \cdot H_2O$ and 342.9 g/mol

Structural formula:



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

14 CLINICAL TRIALS

The information on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute LD₅₀ determinations in the mouse and rat were as follows:

	Route of Administration	Species	Acute LD₅₀ ±s.e. mg/kg at 24 hours
Bupivacaine HCl 0.50%	I.V.	Mouse	7.1 ± 0.6
	I.V.	Rat	6.2 ± 0.5
	S.C.	Mouse	63 ± 7
	S.C.	Rat	63 ± 9

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).

17 SUPPORTING PRODUCT MONOGRAPHS

1. MARCAINE (Sterile Solution / 2.5 mg/mL, 5 mg/mL and 7.5 mg/mL / bupivacaine hydrochloride); MARCAINE SPINAL (Sterile Solution / 7.5 mg/mL / bupivacaine hydrochloride in dextrose injection); MARCAINE E (Sterile Solution/ 2.5 mg/mL and 5 mg/mL / bupivacaine hydrochloride and epinephrine bitartrate (9.1 mcg/mL)), submission control 269793, Product Monograph, Pfizer Canada ULC., (MAY 11, 2023)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Bupivacaine Hydrochloride Injection, USP

Read this carefully before you start taking **Bupivacaine Hydrochloride Injection, USP** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Bupivacaine Hydrochloride Injection, USP**

Serious Warnings and Precautions

Bupivacaine Hydrochloride Injection, USP is for healthcare professional use only. Your healthcare professional will be trained in the management and care of local anesthetics, such as Bupivacaine Hydrochloride Injection, USP. They will prepare and give you Bupivacaine Hydrochloride Injection, USP in a hospital setting with the adequate equipment for the proper management of unwanted side effects. They will also monitor your health throughout the treatment.

What is Bupivacaine Hydrochloride Injection, USP used for?

Bupivacaine Hydrochloride Injection, USP is used in adults and children (2 years of age and older) to prevent or relieve pain to an area of the body. This can include before and after a surgery, during labour, or after a sudden injury.

How does Bupivacaine Hydrochloride Injection, USP work?

Bupivacaine Hydrochloride Injection, USP belongs to a group of medicines known as local anesthetics. They act by temporarily preventing the nerves around the site of injection from transmitting sensations of pain, heat, or cold. However, you may still experience sensations such as pressure and touch. In this way the nerves are numbed in the part of the body, which will be subjected to surgery.

What are the ingredients in Bupivacaine Hydrochloride Injection, USP?

Medicinal ingredients: Bupivacaine Hydrochloride

Non-medicinal ingredients: hydrochloric acid and/or sodium hydroxide, sodium chloride, and water for injection. Multidose vials also contain methylparaben (as a preservative).

Bupivacaine Hydrochloride Injection, USP comes in the following dosage forms:

Bupivacaine Hydrochloride Injection, USP:

- Single dose vials: 0.25% (2.5 mg/mL), and 0.75% (7.5 mg/mL) solution.

- Multidose vials: 0.5% (5 mg/mL) solution.

Do not use Bupivacaine Hydrochloride Injection, USP if:

- you are allergic to bupivacaine, other anesthetics that end with “-caine”, or any of the other ingredients in Bupivacaine Hydrochloride Injection, USP. If you are unsure ask your healthcare professional.
- you are planning to use Bupivacaine Hydrochloride Injection, USP for intravenous regional anesthesia (Bier block) that can be used to reduce pain in the arms or legs.
- you are currently receiving or planning to receive anesthetics (medicines used to prevent the feeling of pain during surgeries/operations) during labour.
- you are in severe shock (a blood circulation failure), have a heart block (electrical signal that controls the heart from beating is partially or completely blocked), and have a severe reaction to an infection (sepsis) near the proposed site of injection for the Bupivacaine Hydrochloride Injection, USP injection.

In addition:

- Do not use Bupivacaine Hydrochloride Injection, USP multidose vials that contain methylparaben (as a preservative):
 - for epidural anesthesia (injection into the sac of fluid around your spinal cord called the epidural space);
 - for spinal anesthesia (into the fluid around your spinal cord and brain);
 - intraocularly (into the eye);
 - retroocularly (behind the eye); or
 - if you are allergic to substances known as para-aminobenzoic acid (PABA), methylparaben, other parabens;

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Bupivacaine Hydrochloride Injection, USP. Talk about any health conditions or problems you may have, including if you:

- have heart, blood vessel, or blood circulation problems;
- have kidney problems;
- have liver problems;
- have thyroid gland problems;
- have high blood pressure;
- have inflamed or infected skin tissue;
- have diabetes;
- have a condition that causes weakness or frailty;
- have recently had a surgery or planning to have a surgery;
- are over 65 years of age or under 18 years of age;

- are severely ill;
- are pregnant or are planning to become pregnant;
- are breastfeeding or planning to breastfeed. Bupivacaine can pass into your breast milk.

Other warnings you should know about:

Driving and using machines: Bupivacaine Hydrochloride Injection, USP may temporarily interfere with your reactions and coordination. Before you do tasks that may require your attention, you should wait until you know how you react to your treatment.

Testing and monitoring: Your healthcare professional will regularly monitor your health throughout your treatment. This may include monitoring:

- how you react to your dose;
- your blood pressure, heart rate, heart rhythm, and heart and blood vessel functions;
- your breathing and lung function;
- your vision.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Bupivacaine Hydrochloride Injection, USP:

- anesthetics, medicines used to prevent pain during surgery (e.g., lidocaine, ropivacaine, mepivacaine, chloroprocaine, prilocaine, halothane, cyclopropane, trichloroethylene, and enflurane).
- antiarrhythmics, medicines used to treat abnormal heartbeat and heart rhythms (e.g., procainamide, disopyramide, tocainide, mexiletine, flecainide, and amiodarone).
- antidepressants, medicines used to treat depression (e.g., monoamine oxidase (MAO) inhibitors, triptyline, and imipramine).
- beta-blockers, medicines used to lower blood pressure (e.g., propranolol).
- H₂-antagonists, medicines used to treat ulcers (e.g., cimetidine and ranitidine).
- medicines containing a substance called ergot.
- neuroleptics, medicines used to treat mental health disorders (e.g., phenothiazines and butyrophenones).
- sedatives, medicines that can increase drowsiness.
- vasoconstrictors, medicines used to treat low blood pressure.

How to take Bupivacaine Hydrochloride Injection, USP:

Your healthcare professional will prepare and give you Bupivacaine Hydrochloride Injection, USP in a healthcare setting. The site of injection will be determined by your healthcare professional as follows:

retrobulbar (behind the eye), epidural (into the space around your spinal cord), or block/infiltration (near a nerve or group of nerves).

For children (2 to 18 years of age), the route of administration may also be determined by age.

Usual dose:

Bupivacaine Hydrochloride Injection, USP will be administered by your healthcare professional. This may depend on:

- your age and weight,
- your medical condition,
- how you respond to the treatment,
- if you take other medicines, and/or
- the type of surgery.

The lowest effective dose of Bupivacaine Hydrochloride Injection, USP will be used.

Overdose:

Your healthcare professional will monitor you for signs and symptoms of an overdose. If an overdose is suspected, your healthcare professional will act accordingly to manage your side effects.

The symptoms of an overdose may include:

- hearing disturbances,
- lightheadedness,
- muscular twitching or tremors,
- numbness of the lips and around the mouth,
- numbness of the tongue,
- seizures
- speech changes,
- tingling in the ears,
- trembling,
- unconsciousness
- visual disturbances

If you notice any of these symptoms, tell your healthcare professional right away.

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

What are possible side effects from using Bupivacaine Hydrochloride Injection, USP?

These are not all the possible side effects you may have when taking Bupivacaine Hydrochloride Injection, USP. If you experience any side effects not listed here, tell your healthcare professional.

Side effects of Bupivacaine Hydrochloride Injection, USP may include:

- anxiety
- chills,
- headache,
- numbness,
- pins and needles,
- restlessness,
- ringing in the ears.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, or fatigue (may occur when you go from lying or sitting to standing up).		✓	
COMMON			
Arrhythmia (abnormal heart rhythms): rapid, slow, or irregular heartbeat.			✓
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness, fainting, chest pain, chest pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse, or heart palpitations.		✓	
Urinary retention (inability to pass urine or empty the bladder): hard to start the flow of urine, slow urine stream, or unable to completely empty your bladder when urinating.		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Allergic reaction: difficulty swallowing, wheezing, drop in blood pressure, feeling sick to your stomach, vomiting, hives, rash, swelling of the face, lips, tongue or throat, itching, shortness of breath, difficulty breathing, red skin, fast heart rate, sneezing, nausea, dizziness, or sweating more than normal.			✓
Nerve problems: back pain, loss or impairment of motor and sensory function, paralysis, decreased sensitivity or feeling in the skin, or other sensory disturbances.			✓
RARE			
Cardiac arrest (heart suddenly stops beating): fatigue, loss of consciousness, dizziness, difficulty breathing, nausea, chest pain, or heart palpitations.			✓
UNKNOWN FREQUENCY			
Liver problems: yellowing of the skin and eyes (jaundice), dark urine, bleeding easily, swollen stomach, mental disorientation, confusion, sleepiness, coma, fatigue, loss of appetite, itching, stomach pain, nausea, or rash.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting 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.

Storage:

Your healthcare professional will store Bupivacaine Hydrochloride Injection, USP at 15°C to 30°C. Do not freeze.

Keep out of reach and sight of children.

If you want more information about Bupivacaine Hydrochloride 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.baxter.ca, or by calling 1-888-719-9955.

This leaflet was prepared by Baxter Corporation, Mississauga, Ontario, L5N 0C2.

Baxter is a registered trademark of Baxter International Inc.

Last Revised: December 6, 2023