PRODUCT MONOGRAPH

JAMP-Bupivacaine

Bupivacaine Hydrochloride Injection USP

2.5 mg/mL and 5 mg/mL Bupivacaine Hydrochloride
(as bupivacaine hydrochloride monohydrate)

Sterile Solution

Local Anesthetic

JAMP Pharma Corporation 1380-203 newton Boucherville, Québec J4B 5H2 Control No. : 178342	Date of Preparation : October 21, 2014

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Parenteral	Bupivacaine Hydrochloride Injection USP Sterile Solution 2.5 mg/mL and 5 mg/mL bupivacaine hydrochloride (as monohydrate)	Sodium chloride, sodium hydroxide and/or hydrochloric acid and water for injection. Multidose vials contain methylparaben as a preservative.

INDICATIONS AND CLINICAL USE

Adults (> 18 years of age):

JAMP-Bupivacaine is indicated for the production of local or regional anaesthesia 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.

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

JAMP-Bupivacaine 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 injections.

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

- In obstetric paracervical block anaesthesia. Use of other local anaesthetics 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.

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 OFCARDIOPULMONARY 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.

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. JAMP-Bupivacaine **should not be used for postoperative intra-articular infusion** (See DOSAGE AND ADMINISTRATION).

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

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

Major peripheral nerve blocks may imply the administration of a large volume of local anaesthetic 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 anaesthetic procedures should be carried out sufficiently away from an inflamed region. Injections should not be performed through inflamed tissue or when there is sepsis at or near the injection site.

Cardiovascular

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

There have been reports of cardiac arrest or death during use of bupivacaine for epidural anaesthesia 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 anaesthetic procedures that may have resulted in high systemic concentrations of bupivacaine.

Epidural anaesthesia 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 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, attempt 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 anaesthesia should be used with caution in patients with impaired cardiovascular function.

Injection in Head and Neck Area

Relatively small doses of local anesthetics injected into the head and neck area, including retrobulbar and stellate ganglion blocks, may produce adverse reactions similar to systemic

toxicity seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care.

Confusion, convulsions, respiratory depression and/or respiratory arrest and cardiovascular stimulation or depression leading to cardiac arrest have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. They may also be due to puncture of the dural sheath of the optic nerve during retrobulbar block with diffusion of any local anesthetic along the subdural space to the midbrain. Patients receiving these blocks should remain under constant observation and monitoring for their cardiac and pulmonary functions. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded (see **DOSAGE AND ADMINISTRATION**).

Ophthalmic Surgery

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

Clinicians who perform retrobulbar blocks should be aware that there have been reports of respiratory arrest following local anaesthetic injection. Prior to retrobulbar block, as with all other regional procedures, the immediate availability of equipment, drugs, and personnel to manage respiratory arrest or depression, convulsions, and cardiac stimulation or depression should be assured (see also **WARNINGS AND PRECAUTIONS, Injection in Head and Neck Area**). As with other anesthetic procedures, patients should be constantly monitored following ophthalmic blocks for signs of these adverse reactions, which may occur following relatively low total doses. A concentration of 0.75% bupivacaine is indicated for retrobulbar block; however, this concentration is not indicated for any other peripheral nerve block, including the facial nerve, and not indicated for local infiltration, including the conjunctivia.

Retrobulbar injections of local anaesthetics 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 anaesthetic and the duration of exposure of the tissue to the local anaesthetic. For this reason, as with all local anaesthetics, the lowest effective concentration and dose of local anaesthetic should be used. Vasoconstrictors and other additives may aggravate tissue reactions and should be used only when indicated.

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 a void 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.

Hyper-Sensitivity

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

Special Populations

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

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

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

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

Labour and Delivery: JAMP-Bupivacaine 2.5 mg/mL or 5 mg/mL can be used at term for obstetrical anesthesia or analgesia.

Bupivacaine is contraindicated for obstetrical paracervical block anesthesia (see **WARNINGS AND PRECAUTIONS**). Local anaesthetics 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 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.

Epidural anaesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Epidural anaesthesia 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 2.5 mg/mL has been shown to interfere less than the 0.5 mg/mL solution. Obstetrical anaesthesia may increase the need for forceps assistance.

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

Nursing Women: Bupivacaine is excreted in the breast milk, but in such small quantities that there is generally no risk of affecting the infant at therapeutic doses.

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

Until further experience is gained, the following restrictions apply to the use of JAMP-Bupivacaine: (a) isotonic bupivacaine solutions with are not recommended for spinal use.

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 under ventilation 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, 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 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.

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 pre-operative medication.

DRUG INTERACTIONS

Drug-Drug Interactions
See **WARNINGS AND PRECAUTIONS** concerning solutions containing a vasoconstrictor.

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

Local 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.

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 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.

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.

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.

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

- 2.5 mg/mL, when used for caudal, epidural, or peripheral nerve block, produces incomplete motor block. Should be used for operations in which muscle relaxation is not important, or when another means of providing muscle relaxation is used concurrently. Onset of action may be slower than with the 5 mg/mL.

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

There have been adverse event reports of irreversible chondrolysis in patients receiving intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures. JAMP-Bupivacaine 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. 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 5 mg/mL and 2.5 mg/mL concentrations of isotonic JAMP-Bupivacaine are recommended at term for obstetrical anesthesia and analgesia.

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

To avoid intravascular injection, aspiration should be repeated prior to and during administration of the main dose, which should be injected slowly or in incremental doses, at a rate of 25-50 mg/min, while closely observing the patient's vital function and maintaining verbal contact. An inadvertent intravascular injection may be recognized by a temporary increase in heart rate and an accidental intrathecal injection by signs of a spinal block. If toxic symptoms occur, the injection should be stopped immediately.

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

Table 1 Dosage recommendations in adults.

TYPE OF BLOCK	CONC. (mg/mL)	EACH DOSE[a] mL	mg	ONSET (min.)	DURATION (h) Without epinephrine	INDICATION
Local infiltration	2.5 5	up to 60 [b] up to 30 [b]	up to 150[b] up to 150[b]	1-3 1-3	3-4 4-8	Surgical operations and postoperative analgesia.
Lumbar epidural	2.5 5	6-15 15-30	15-37.5 75-150	2-5 15-30	1-2 2-3	Labour and postoperative pain relief. Surgical operations including Caesarean Section.
Thoracic epidural	2.5	5-15	12.5- 37.5 25-50	10-15	1.5-2	Surgical operations.

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

a For epidural blocks, dose includes test dose.

b No more than 400 mg in 24 hours. There have been post-marketing reports of irreversible chondrolysis in patients receiving post-operative intra-articular infusion of local anaesthetics. Bupivacaine Hydrochloride for Injection USP is not approved for this use. (see WARNINGS AND PRECAUTIONS, General).

c Without ephinephrine.

d See **WARNINGS AND PRECAUTIONS**

Children:

Until further experience is gained, bupivacaine is not recommended for children younger than two years of age. The following restrictions apply to the use of JAMP-Bupivacaine for children over two years of age: (a) isotonic bupivacaine solutions are not recommended for spinal use.

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 (mg/mL)	each dose	
		mL/kg	mg/kg
Local infiltration	2.5	Up to 0.8	Up to 2
	5	Up to 0.4	Up to 2

Caudal epidural[b] -Lumbosacral -Thoracolumbar	 2.5 2.5	 0.5 0.6- 1.0	 1.25[c] 1.5- 2.5[c]
Lumbar epidural	2.5 5	0.5-1.0 0.3-0.5	1.25- 2.5 1.5-2.5
Dorsal (penile)	2.5[a] 5 [a]	0.1-0.2 0.1-0.2	0.25-0.5 0.5-1.0

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

[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 Anaesthesia

When an epidural dose is to be injected, a test dose of a local anaesthetic is recommended (see **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 **CONTRAINDICATIONS**).

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. Epinephrine (0.1-0.2 mg intravenous or intracardial injections) should be given as soon as possible and repeated, if necessary. A successful resuscitation may require prolonged efforts.

The supine position is dangerous in pregnant women at term because of aortocaval compression by the gravid uterus. Therefore, during treatment of systemic toxicity, maternal hypotension or foetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels should be accomplished. Resuscitation of obstetrical patients may take longer than resuscitation of nonpregnant patients and closed-chest cardiac compression may be ineffective. Rapid delivery of the foetus may improve the response to resuscitative efforts.

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

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

ACTION AND CLINICAL PHARMACOLOGY

Bupivacaine is a long-acting, amide-type local 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. The presence of epinephrine may prolong the duration of action for infiltration and peripheral nerve blocks but has less marked effect on epidural blocks.

JAMP-Bupivacaine 5 mg/mL 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 anaesthetizing large nerves. When used in low concentrations, i.e., 2.5 mg/mL, there is less effect on motor nerve fibres and the duration of action is shorter.

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 hydrochloride for caudal, epidural, or peripheral nerve block in man, peak levels of bupivacaine hydrochloride 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. JAMP-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 JAMP-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 JAMP-Bupivacaine at 20-25°C. Do not freeze.
Do not use if solution is coloured or contains a precipitate.
Do not use product if solution shows haziness, particulate matter, discolouration, or leakage

SPECIAL HANDLING INSTRUCTIONS

Isotonic Solutions

These solutions are not for spinal anesthesia.

JAMP-Bupivacaine solutions may be autoclaved. Autoclave at 15-pound pressure, 121°C (250°F) for 15 minutes. Do not use if solution is discoloured or contains a precipitate.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

The solubility of bupivacaine is limited at pH > 6.5. This must be taken into consideration when alkaline solutions, i.e., carbonates, are added since precipitation might occur.

Composition and Packaging
Composition

JAMP-Bupivacaine, 2.5 mg/mL - with preservative

Each mL contains: Bupivacaine hydrochloride USP 2.5 mg. Non-medicinal ingredients: 1 mg of Methyl Paraben (as preservative), 8.6 mg of Sodium Chloride, Sufficient quantity of Sodium Hydroxide and/or Hydrochloric Acid added to adjust pH and Water for Injection.

JAMP-Bupivacaine, 5 mg/mL - with preservative

Each mL contains: Bupivacaine hydrochloride USP 2.5 mg. Non-medicinal ingredients: 1 mg of Methyl Paraben (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.

Packaging

- **JAMP-Bupivacaine, 2.5 mg/mL**
  Multiple-dose vials of 50 mL (with methylparaben as preservative) box of 1

- **JAMP-Bupivacaine, 5 mg/mL**
  Multiple-dose vials of 50 mL (with methylparaben as preservative) box of 1

PART II: SCIENTIFIC INFORMATION

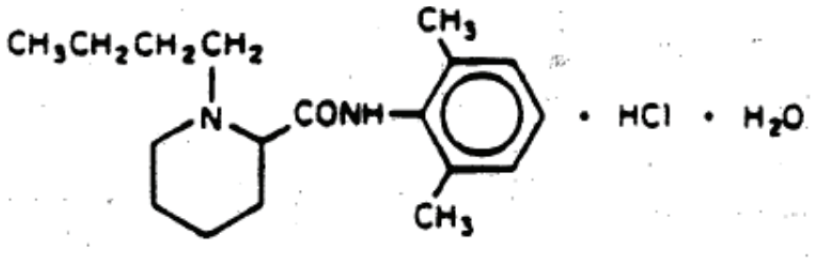
PHARMACEUTICAL INFORMATION

Bupivacaine Hydrochloride

Proper Name: Bupivacaine Hydrochloride Monohydrate
Chemical name: (2RS)-1-Butyl- N-(2, 6-dimethylphenyl)piperidine-2-carboxamide hydrochloride monohydrate

Molecular formula and molecular mass: $C_{18}H_{29}ClN_2O \cdot H_2O$ 342.90

Structural formula:



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

DETAILED PHARMACOLOGY

Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

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

In metabolic studies in the rat, subcutaneous doses of C^{14} - labeled 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 5 mg/mL	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).

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PART III: CONSUMER INFORMATION

JAMP-Bupivacaine

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

ABOUT THIS MEDICATION

What the medication is used for:
JAMP-Bupivacaine is used to anesthetize part of the body for surgical operations and also for pain relief, and can be used:

- to anaesthetize the area of the body where surgery is to be performed;
- to provide pain relief in labour and after surgery or acute injury.

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

When it should not be used:
JAMP-Bupivacaine 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)

JAMP-Bupivacaine (multi-dose vials) should not be used in patients who are allergic to methylparaben, other parabens or PABA.

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

What the medicinal ingredient is:
Bupivacaine Hydrochloride

What the non-medicinal ingredients are:
JAMP-Bupivacaine contains sodium chloride, Sodium hydroxide and/or Hydrochloric acid added to adjust the pH and water for injection. Multidose vials contain methylparaben as a preservative.

What dosage form it comes in:
JAMP-Bupivacaine is available as follows:

- **JAMP-Bupivacaine, 2.5 mg/mL**
  - Multiple-dose vials of 50 mL (with methylparaben as preservative) box of 1
- **JAMP-Bupivacaine, 5 mg/mL**
  - Multiple-dose vials of 50 mL (with methylparaben as preservative) box of 1

WARNINGS AND PRECAUTIONS

You should talk to your doctor prior to surgery:

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

INTERACTIONS WITH THIS MEDICATION

Many drugs interact with JAMP-Bupivacaine. 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 JAMP-Bupivacaine may increase the risk of serious side effects.

PROPER USE OF THIS MEDICATION

Usual dose:
JAMP-Bupivacaine should be administered by a doctor. The dose given is decided by the doctor based on the clinical need and your physical condition.

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

The first signs that too much JAMP-Bupivacaine has been given usually take the form of lightheadedness, numbness of the lips and around 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 misplaced injection, trembling, seizures or unconsciousness may occur.

If the administration of JAMP-Bupivacaine is stopped as soon as early signs of overdose appear, the risk of serious adverse effects rapidly decreases.

If you think you have taken too much JAMP-Bupivacaine, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like any medication, JAMP-Bupivacaine 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 JAMP-Bupivacaine is causing an allergic reaction, tell your doctor immediately.**

There are other possible side effects that have been reported for JAMP-Bupivacaine. 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 of 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 JAMP-Bupivacaine (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 cause 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 JAMP-Bupivacaine include:

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

If too much JAMP-Bupivacaine is given into the spinal fluid, the whole body may become numbed (anesthetized).

This is not a complete list of side effects. For any unexpected effects while taking JAMP-Bupivacaine, contact your doctor or pharmacist.

HOW TO STORE IT

- Store JAMP-Bupivacaine at 20-25°C. Do not freeze.
- Do not use if solution is coloured or contains a precipitate.
- Do not use product if solution shows haziness, particulate matter, discolouration, or leakage

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report Online at www.healthcanada.gc.ca/medeffect
Call toll-free telephone: 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789
- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701C
  Ottawa ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document can be found at: www.mylan.ca.

The full Product Monograph prepared for health professionals can be obtained by contacting the sponsor:

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Last revised: October 21, 2014