PRODUCT MONOGRAPH

SENSORCAINE® FORTE
Bupivacaine Hydrochloride and Epinephrine Injection USP
0.5 %
(bupivacaine hydrochloride 0.5 % with epinephrine 1:200.000 as bitartrate)

Local Anesthetic

Dentsply Canada
161 Vinyl Court
Woodbridge, Ontario
L4L 4A3

Date of Revision:
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Control#: 097993

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THERAPEUTIC CLASSIFICATION

Local Anesthetic

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

As with other local anesthetics, SENSORCAINE FORTE (bupivacaine hydrochloride) 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. Local anesthetics of the amide type are thought to act within the sodium channels of the membrane.

Onset and Duration of Action

As with other local anesthetics, the onset and duration of action depends on the injection site, the route of administration, and the concentration and volume of anesthetic (see Table 1, 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 potent analgesics is reduced.

SENSORCAINE FORTE has a long duration of action of up to 12 hours after peripheral nerve blocks. The onset of blockade is slower than with lidocaine, especially when anesthetizing large nerves.

Hemodynamics

Bupivacaine, like other local anesthetics, may also have effects on excitable membranes 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 SYMPTOMS AND TREATMENT OF OVERDOSAGE) usually precedes the cardiovascular effects as it occurs at lower plasma concentrations. Direct effects of local anesthetics on the heart include slow conduction, negative inotropism and eventually cardiac arrest.

Pharmacokinetics and Metabolism

The rate of systemic absorption 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.

Peak levels of bupivacaine in the blood are reached in 20 to 45 minutes, depending on injection site and type of block. A decline to insignificant levels is achieved during the next three to six hours. Epinephrine may decrease the rate of absorption.

Bupivacaine has a total plasma clearance of 0.58 L/min and a volume of distribution at steady state of 73 L. The elimination half-life of bupivacaine in adults is 2.7 hours. The elderly may have a prolonged half-life.

In adults the protein-binding capacity of bupivacaine is high at 96%. Generally, the lower the plasma concentration of drug, the higher the percentage of drug bound to plasma proteins. Bupivacaine is mainly bound to alpha-1-acid glycoprotein.

An increase in alpha-1-acid glycoprotein, which occurs postoperatively after major surgery, may cause an increase in the total plasma concentration of bupivacaine. The level of free drug will remain the same. This explains why total plasma concentrations above the apparent toxic threshold level of 2.6 – 3.0 mg/L are well tolerated.

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

Bupivacaine is primarily metabolized in the liver via biotransformation and conjugation with glucuronic acid. The major metabolite of bupivacaine is 2,6-pipecoloxylidine (PPX). The kidney is the main excretory organ for most local anesthetics and their metabolites. About 6% of bupivacaine is excreted in the urine as unchanged drug in 24 h and approximately 5% as PPX.

INDICATONS AND CLINICAL USE

SENSORCAINE FORTE (bupivacaine hydrochloride and epinephrine 1:200,000) is indicated for the production of local anesthesia for dental procedures by infiltration injection or nerve block in adults. SENSORCAINE FORTE is not recommended for use in children under 12 years.

CONTRAINDICATIONS

SENSORCAINE FORTE (bupivacaine hydrochloride) is contraindication in patients with a known hypersensitivity to bupivacaine or to any local anesthetic agent of the amide type or to other components of bupivacaine solutions.

WARNINGS

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

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

It is essential that aspiration for blood be done prior to injecting any local anesthetic, both the original dose and all subsequent doses, to avoid intravascular injection. However, a negative aspiration does not ensure against an intravascular injection.

SENSORCAINE FORTE contains epinephrine and, therefore, should be used with caution in patients whose medical history and physical evaluation suggest the existence of untreated hypertension, ischemic heart disease, cerebral vascular insufficiency, heart block, peripheral vascular disorder, poorly controlled thyrotoxicosis and diabetes.

SENSORCAINE FORTE contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

PRECAUTIONS

The safety and effectiveness of local anesthetics depend on proper dosage, correct technique, adequate precautions and readiness for emergencies. Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use (see WARNINGS and ADVERSE REACTIONS).

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

Injection of repeated doses of local anesthetics may cause significant increases in plasma levels with each repeated dose due to slow accumulation of the drug or its metabolites or to slow metabolic degradation. Tolerance to elevated blood levels varies with the physical condition of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with their age and physical condition.

Local anesthetics should be used with caution in patients in poor general condition due to aging or other compromising factors such as partial or complete heart conduction block, advanced liver disease, or severe renal dysfunction (see also WARNINGS). Dosage should be adjusted accordingly.

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

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

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.

Local anesthetic procedures should be used with care in inflamed regions. Injections should not be performed through inflamed tissue nor when there is sepsis at or near the injection site.

Because of the long duration of anesthesia, when SENSORCAINE FORTE is used for dental injections, patients should be cautioned about the possibility of inadvertent trauma to tongue, lips, and buccal mucosa and advised not to chew solid foods or test the anesthetized area by biting or probing.

Changes in sensorium such as excitation, disorientation, drowsiness, may be early indications of a high blood level of the drug and may occur following inadvertent intravascular administration or rapid absorption of SENSORCAINE FORTE. Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Small doses of local anesthetics injected into the head and neck area, including dental blocks, may produce adverse reactions caused by inadvertent injection to an artery. These adverse reactions may be similar to systemic toxicity seen with unintentional intravascular injections of larger doses. 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. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded (see DOSAGE AND ADMINISTRATION).

Drug Interactions

See WARNINGS concerning solutions containing a vasoconstrictor.

SENSORCAINE FORTE should be used with caution in patients receiving other local anesthetics since toxic effects are additive. SENSORCAINE FORTE should also be used with caution with other amide-type local anesthetics such as lidocaine, ropivacaine, mepivicaine and prilocaine, and structurally related agents such as the antiarrhythmics, procainamide, disopyramide, tocainide and flecainide.

Bupivacaine solutions containing 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. Likewise, these solutions should be used with extreme caution in patients receiving monoamine oxidase inhibitors (MAO) or antidepressants of the triptyline or imipramine types, because severe prolonged hypertension may result. In situations when concurrent therapy is necessary, careful patient monitoring is essential. Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

If sedatives are employed 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.

SENSORCAINE FORTE should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Solutions containing epinephrine should be used with caution in patients undergoing general anesthesia with inhalation agents such as halothane, due to the risk of serious dose-related cardiac arrhythmias. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Prior use of chloroprocaine, or any other local anesthetic, 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.

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.

Use in Pregnancy

It is reasonable to assume that a large number of pregnant women and women of childbearing age have been bupivacaine. No specific disturbances to the reproductive process have so far been reported, e.g., no increased incidence of malformations. However, there are no adequate and well-controlled studies in pregnant women of the effect of bupivacaine on the developing fetus and therefore, SENSORCAINE FORTE, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

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

Use in Children

SENSORCAINE FORTE is not recommended for use in children under 12 years.

ADVERSE REACTIONS

Reactions to SENSORCAINE FORTE (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.

Acute systemic toxicity from local anesthetics is generally dose-related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance, or from inadvertent intravascular injection. Most commonly, the acute adverse experiences originate from the central nervous and cardiovascular systems.

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, 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, 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, PRECAUTIONS, and OVERDOSAGE sections).

Allergic

Allergic type reactions are rare 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 edema (including laryngeal edema), 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 it is also dependent upon the particular drug used, the route of administration and the physical condition of the patient. Nerve trauma, neuropathy and spinal cord dysfunction (e.g., anterior spinal artery syndrome, arachnoiditis, cauda equina syndrome) have been associated with regional anesthesia. Neurological effects may be related to local anesthetic techniques, with or without a contribution from the drug.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Acute systemic toxicity from local anesthetics is generally related to high plasma levels encountered during therapeutic use, or intravascular injection, exceptionally rapid absorption or overdosage and originates mainly in the central nervous and the cardiovascular systems (see ADVERSE REACTIONS, WARNINGS, and PRECAUTIONS).

Symptoms

With accidental intravascular injections, the toxic effect will be obvious within 1-3 minutes, while with overdosage, peak plasma concentrations may not be reached for 20-30 minutes depending on the site of injection, with signs of toxicity thus being delayed.

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are circumoral paresthesia, numbness of the tongue, lightheadedness, hyperacusis and tinnitus. Visual disturbance and muscular 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 apnea may occur. Acidosis increases the toxic effects of local anesthetics.

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

Cardiovascular effects may be seen in cases with high systemic concentrations. Severe hypotension, bradycardia, arrhythmia and cardiac arrest may be the result in such cases.

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. Usually these will be preceded or accompanied by major CNS toxicity i.e. convulsions, but in rare cases cardiac arrest has occurred without prodromal CNS effects. In patients under heavy sedation or receiving a general anesthetic, prodromal CNS symptoms may be absent.

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 MANGEMENT OF SYSTEMIC TOXIC REACTIONS CONSISTS OF IMMEDIATE ATTENTION TO THE ESTABLISHMENT AND MAINTENANCE OF A PATENT AIRWAY AND ASSISTED OR CONTROLLED VENTILATION WITH OXYGEN AND A DELIVERY SYSTEM CAPABLE O PERMITTING IMMEDIATE POSITIVE AIRWAY PRESSURE BY MASK. This may prevent convulsions if they have not already occurred.

If necessary, use drugs to control the convulsions. An anticonvulsant should be given i.v. if the convulsions do not stop spontaneously in 15-20 seconds. Thiopental 100-150 mg i.v. will abort the convulsions rapidly. Alternatively diazepam 5-10 mg i.v. may be used, although its action is slower. Succinylcholine will stop the muscle convulsions rapidly, but will require tracheal intubation and controlled ventilation, and should only be used by those familiar with these procedures.

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.

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.

The supine position is dangerous in pregnant women at term because of aorto-caval compression by the gravid uterus. Therefore, during treatment of systemic toxicity, maternal hypotension or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels 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 fetus may improve the response to resuscitative efforts.

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

DOSAGE AND ADMINISTRATION

The lowest dosage of SENSORCAINE FORTE 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. The volume of drug used will affect the extent of spread of anesthesia.

SENSORCAINE FORTE contains epinephrine which prolongs the anesthetic action. The dosages in Table 1 are recommended as a guide for use in the average adult. 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 for SENSORCAINE FORTE

TYPE OF BLOCK	CONC(%)	EACH DOSE[a]		ONSET	INDICATION
		mL	mg	(min.)	
Dental Anesthesia				2-10	Dental anesthesia.
-Infiltration	0.5[a]	1-1.8	5-9		
-Nerve Block	0.5[a]	1.8-3.6	9-18		

[a]With epinephrine 1:200,000 (5 µg/mL).

SENSORCAINE FORTE is recommended for infiltration and block injection in the maxillary and mandibular areas when a longer duration of local anesthetic action is desired, such as for oral surgical procedures generally associated with significant postoperative pain. The average dose of 1.8 mL (9 mg) per injection site will usually be sufficient (Table 1); an occasional second dose of 1.8 mL (9 mg) may be used if necessary to produce adequate anesthesia after making allowances for 2 to 10 minutes onset time. The lowest effective dose should be employed and time should be allowed between injections. It is recommended that the total dose for all injection sites, spread out over a single dental sitting should not ordinarily exceed 90 mg for a healthy adult patient (ten 1.8 mL injections of SENSORCAINE FORTE). Injections should be made slowly and with frequent aspirations.

Until further experience is gained, SENSORCAINE FORTE in dentistry is not recommended for children younger than 12 years.

PHARMACEUTICAL INFORMATION

Drug Substance

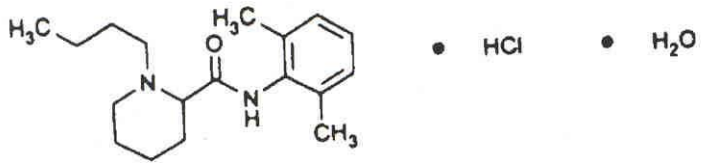
Bupivacaine Hydrochloride

Proper Name: bupivacaine hydrochloride

Chemical Name: 2-piperidinecarboxamide,1-butyl-*N*-(2,6-dimethylphenyl), monohydrochloride, monohydrate

Molecular Formula: $C_{18}H_{28}N_2O.HCl.H_2O$

Structural Formula:



Molecular Weight: 342.91

Description: White, odorless, crystalline powder. Freely soluble in water and in alcohol. Slightly soluble in chloroform and in acetone. Melting point approximately 248°F, with decomposition.

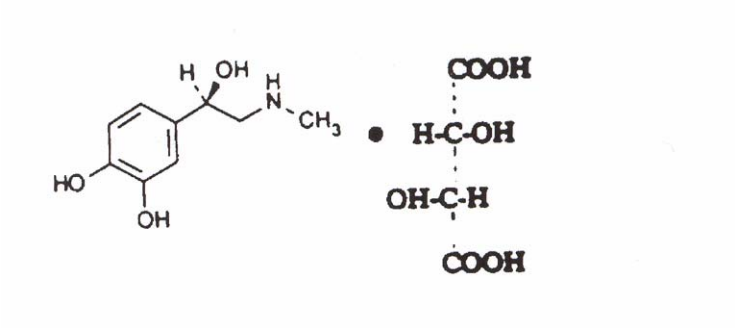
Epinephrine

Proper Name: epinephrine bitartrate

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

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

Structural Formula:



Molecular Weight: 333.3

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

Dosage Form

SENSORCAINE FORTE is a sterile isotonic solution.

The pK_a of bupivacaine (8.1) is similar to that of lidocaine. However, bupivacaine possesses a greater degree of lipid solubility and is protein bound (95%) to a greater extent than lidocaine (64%).

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

Composition

Active:

	0.5%
Bupivacaine hydrochloride mg/mL	5

SENSORCAINE FORTE contains epinephrine bitartrate equivalent to 1:200,000 or 5 μg/mL base.

Non-medicinal:

	mg/mL
sodium chloride (for isotonicity)	8
sodium metabisulfite (as an antioxidant)	0.55
citric acid (as a buffer)	0.2
water for injection	q.s.

sodium hydroxide and/or hydrochloric acid to adjust to pH to 3.3 – 5.5

Stability and Storage Recommendations

Store SENSORCAINE FORTE at 15 –30°C. Protect from light. Do not use if solution is pinkish or darker than slightly yellow or if it contains precipitate.

Due to the heat sensitivity of epinephrine, SENSORCAINE FORTE should not be autoclaved.

SENSORCAINE FORTE is without preservative and is for single use only. Discard unused portion.

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

The dental cartridges of SENSORCAINE FORTE may be disinfected with either isopropyl alcohol (91%) or ethyl alcohol (70%).

AVAILABILITY OF DOSAGE FORMS

SENSORCAINE FORTE is available in cartons of 50 dental cartridges (1.8 mL).

PHARMACOLOGY

The mechanism of action for bupivacaine hydrochloride as for other local anesthetics is that it blocks the generation and the conduction of nerve impulses. The threshold potential of the nerve fibre is mainly unchanged and there is a decrease in rate of rise of the action potential. When the depolarization is not sufficient to reach the threshold potential, the consequence will be conduction block.

After injection of bupivacaine in humans, peak blood levels are reached in 30 to 45 minutes depending on injection site and type of block. A decline to insignificant levels is achieved during the next three to six hours. The elimination half-life of bupivacaine in adults is 2.7 hours and in neonates it is prolonged up to eight hours.

As for other local anesthetics, bupivacaine is biotransformed in the liver by conjugation with glucuronic acid. The major metabolite is 2,6-pipecoloxylidine. Bupivacaine and the metabolites are excreted mainly via the kidneys.

TOXICOLOGY

Acute toxicity (LD_{50}) after single intravenous and subcutaneous administration in mice and rats and after intraperitoneal administration in mice are shown in Table 2. Lethal doses after intravenous injection in rabbits and dogs are shown in Table 3.

Table 2. Lethal toxicity in mice and rats after single administration of bupivacaine.

Animals	No.	Route of Administration	LD_{50} (mg/kg) and Standard Error
Mice (NMRI)	36	i.v.	7.3 ± 1.0
	31	s.c.	53 ± 5
Rats (Sprague-Dawley)	36	i.v.	5.6 ± 0.2
	40	s.c.	48 ± 3
Mice (Charles River)	41	i.p.	58.7 ± 2.0

Table 3. Lethal toxicity in rabbits and dogs after administration of bupivacaine.

Animals	No.	Route of Administration	LD_{50} (mg/kg) and Standard Error
Rabbits	8	i.v.	6.9 ± 0.7
Dogs	5	i.v.	20.4[a] ± 2.4

[a] cumulative dose

Seizure threshold for bupivacaine in Rhesus monkeys was found to be 4.4 mg/kg with a mean arterial plasma concentration of 4.5 μg/mL.

Some tissue irritation has been seen in rabbits after intracutaneous administration of bupivacaine (0.2 – 1%). Muscular atrophy appeared after repeated intramuscular injection into one and the same muscle. However, three weeks after administration, the regeneration of the affected muscle appeared to be almost complete.

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