plasma levels and related depression of the myocardium, decreased cardiac output, heartblock, hypotension, bradycardia, ventricular arrhythmias.

Allergic: Sensitivity to the local anesthetic or to other formulation ingredients, such as the antimicrobial preservative methylparaben contained in multiple-dose vials or sulfites in epinephrine containing solutions. These reactions as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly, anaphylactoid-like symptomatology.

Neurologic: The incidences of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon the particular drug used, the route of administration, and the physical status of the patient.

In the practice of caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter or needle may occur. A high spinal is characterized by paralysis of the legs, loss of consciousness, respiratory paralysis, and bradycardia.

Neurologic effects following epidural or caudal anesthesia may include spinal block of varying magnitude hypotension secondary to spinal block; urinary retention; fecal and urinary incontinence; loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities and loss of sphincter control all of which may have slow, incomplete, or no recovery; headache; backache; septic meningitis; meningismus; slowing of labor; increased incidence of forceps delivery; and cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid.

Neurologic effects following other procedures or routes of administration may include persistent anesthesia, paresthesia, weakness, paralysis, all of which may have slow, incomplete, or no recovery.

DOSAGE AND ADMINISTRATION

The dose of any local anesthetic administered varies with the anesthetic procedure, 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, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. The smallest dose and concentration required to produce the desired result should be administered. Dosages of Bupivacaine Hydrochloride should be reduced for elderly and/or debilitated patients and patients with cardiac and/or liver disease. The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should be used when feasible. In recommended doses, Bupivacaine Hydrochloride produces complete sensory block, but the effect on motor function differs among the three concentrations.

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

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

The duration of anesthesia with Bupivacaine Hydrochloride is such that for most indications, 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. These doses may be repeated up to once every three hours. The duration of anesthetic effect may be prolonged by the addition of epinephrine.

These dosages should be reduced for elderly or debilitated patients. Until further experience is gained, Bupivacaine Hydrochloride is not recommended for pediatric patients younger than 12 years.

Use in Epidural Anesthesia: During epidural administration of Bupivacaine Hydrochloride, 0.5% solutions should be administered in incremental doses of 3 mL to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. In obstetrics, only the 0.5% and 0.25% concentrations should be used; incremental doses of 3 mL to 5 mL of the 0.5% solution not exceeding 50 mg to 100 mg at any dosing interval are recommended. Repeat doses should be preceded by a test dose containing epinephrine if not contraindicated. Use only the single-dose ampoules and single-dose vials for caudal or epidural anesthesia; the multiple-dose vials contain a preservative and therefore should not be used for these procedures.

Unused portions of solution not containing preservatives, i.e., those supplied in single-dose ampoules and single-dose vials, should be discarded following initial use. This product should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions which are discolored or which contain particulate matter should not be administered.

Recommended concentration and doses of Bupivacaine Hydrochloride

Type of block	Conc.	Each dose		Motor
		(ml)	(mg)	
Local Infiltration	0.25%[4]	Up to max	Up to max	#
	0.5%[4]	10-20	50-100	Moderate to complete
	0.25%[4]	10-20	25-50	Partial to moderate
Caudal	0.5%[4]	15-30	75-150	Moderate to complete
	0.25%[4]	15-30	37.5-75	Moderate
Peripheral nerves	0.5%[4]	5 to max	25 to max	Moderate to complete
	0.25%[4]	5 to max	12.5 to max	Moderate to complete
Sympathetic	0.25%[4]	2-3	10-15	#
Test Dose	0.5%[4]	15-30		#
Epidural	w/epi		(10-15 micrograms epinephrine)	

1 With continuous (intermittent) techniques, repeat doses increase the degree of motor block. The first repeat dose of 0.5% may produce complete motor block. Intercostal nerve block with 0.25% may also produce complete motor block for intra-abdominal surgery. 2 For single-dose use, not for intermittent epidural technique. Not for obstetrical anesthesia. 3 See Precautions. 4 Solutions with or without epinephrine.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid injection of local anesthetic solution.

Management of Local Anesthetic Emergencies: 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.

Endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated after initial administration of oxygen by mask if difficulty is encountered in the maintenance of a patent airway, or if prolonged ventilatory support (assisted or controlled) is indicated.

If not treated immediately, convulsions with simultaneous hypoxia, hypercarbia, and acidosis plus myocardial depression from the direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest.

Respiratory abnormalities, including apnea, may occur. Underventilation or apnea due to unintentional subarachnoid injection of local anesthetic solution may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest should occur, successful outcome may require prolonged resuscitative 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 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 be accomplished.

The mean seizure dosage of bupivacaine in rhesus monkeys was found to be 4.4 mg/kg with mean arterial plasma concentration of 4.5 mcg/mL. The intravenous and subcutaneous LD50 in mice is 6 mg/kg to 8 mg/kg and 38 mg/kg to 54 mg/kg respectively.

STORAGE

Store below 30°C., protected from light.

PRESENTATION

Anawin* (Bupivacaine Injection B.P.) is available as 2.5 mg/ml in a vial & 5 mg/ml in an ampoule and vial.

MANUFACTURED BY:
NEON LABORATORIES LTD.
Plot No. 29 to 32, 57 & 60, The Palghar Taluka Co-op. Estate Limited, Boisar Road, Palghar (Thane), INDIA.
Regd. Office: 28, Mahal Ind. Estate, M. Caves Road, Andheri (East), Mumbai - 400 093, INDIA.

P37B/1

For the use only of Registered Medical Practitioners or a Hospital or a Laboratory.

BUPIVACAINE INJECTION B.P.
Anawin*

COMPOSITION

Each ml contains:

Bupivacaine Hydrochloride B.P. equivalent to anhydrous Bupivacaine Hydrochloride	2.5 mg/ 5 mg
Sodium Chloride B.P.	8.0 mg
Methylparaben B.P. (as preservative)	1.0 mg
Water for injections B.P.	q.s.

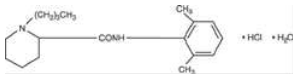
Each ml contains:

Bupivacaine Hydrochloride B.P. equivalent to anhydrous Bupivacaine Hydrochloride	5 mg
Water for injections B.P.	q.s.

DESCRIPTION

Anawin (Bupivacaine Injection B.P) is sterile solution containing 2.5 mg/ 5 mg of anhydrousBupivacaine Hydrochloride. Bupivacaine Hydrochloride is 2-Piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate. The molecular formula is $C_{18}H_{28}N_2O,HCl,H_2O$ and the molecular weight is 342.9. A white crystalline powder that is freely soluble in 95 percent ethanol, soluble in water, and slightly soluble in chloroform or acetone.

It has the following structural formula:



Bupivacaine Hydrochloride Injection is available in sterile isotonic solutions via local infiltration, peripheral nerve block, and caudal and lumbar epidural blocks. Solutions of Bupivacaine Hydrochloride may be autoclaved if they do not contain epinephrine. Solutions are clear and colorless.

Bupivacaine is related chemically and pharmacologically to the aminoacyl local anesthetics. It is a homologue of mepivacaine and is chemically related to lidocaine. All three of these anesthetics contain an amide linkage between the aromatic nucleus and the amino, or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage.

Multiple-dose vials contain methylparaben 1 mg/mL added as a preservative.

Single-dose solutions contain no added bacteriostat or anti-microbial agent and unused portions should be discarded after use.

CLINICAL 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.

Recent clinical reports and animal research suggest that these cardiovascular changes are more likely to occur after unintended intravascular injection of bupivacaine. Therefore, incremental dosing is necessary.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central stimulation is manifested as restlessness, tremors and shivering progressing to convulsions, followed by depression and coma progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited state.

Pharmacokinetics: The rate of systemic absorption of local anesthetics is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution.
The onset of action with Bupivacaine Hydrochloride is rapid and anesthesia is long lasting. The duration of anesthesia is significantly longer with Bupivacaine Hydrochloride than with any other commonly used local anesthetic.
Local anesthetics are bound to plasma proteins in varying degrees. Generally, the lower the plasma concentration of drug the higher the percentage of drug bound to plasma proteins.
Local anesthetics appear to cross the placenta by passive diffusion. 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. Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer. Bupivacaine Hydrochloride with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, nonionized drugs readily enter the fetal blood from the maternal circulation.
Depending upon the route of administration, local anesthetics are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain. The elimination of drug from tissue distribution depends largely upon the ability of binding sites in the circulation to carry it to the liver where it is metabolized.
After injection of Bupivacaine Hydrochloride for caudal, epidural, or peripheral nerve block in man, peak levels of bupivacaine in the blood are reached in 30 to 45 minutes, followed by a decline to insignificant levels during the next three to six hours.
Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic or renal disease, addition of epinephrine, factors affecting urinary pH, renal blood flow, the route of drug administration, and the age of the patient. The half-life of Bupivacaine Hydrochloride in adults is 2.7 hours and in neonates 8.1 hours.
Amide-type local anesthetics such as Bupivacaine Hydrochloride are metabolized primarily in the liver via conjugation with glucuronic acid. Patients with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Pipecoloxylidine is the major metabolite of Bupivacaine Hydrochloride.
The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Only 6% of bupivacaine is excreted unchanged in the urine.

INDICATIONS AND USAGE

Bupivacaine Hydrochloride is indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures. Only the 0.25% and 0.5% concentrations are indicated for obstetrical anesthesia. Bupivacaine Hydrochloride is not recommended for intravenous regional anesthesia
The routes of administration and indicated Bupivacaine Hydrochloride concentrations are:

- local infiltration 0.25%
- peripheral nerve block 0.25% and 0.5%
- sympathetic block 0.25%
- lumbar epidural 0.25%, 0.5%,
- caudal 0.25% and 0.5%

CONTRAINDICATIONS:

Bupivacaine Hydrochloride is contraindicated in obstetrical paracervical block anesthesia. Its use in this technique has resulted in fetal bradycardia and death. In patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type or to other components of Bupivacaine Hydrochloride solutions.

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 INSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. DELAY IN PROPER MANAGEMENT OF DOSERELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE, AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

Local anesthetic solutions containing antimicrobial preservatives, i.e., those supplied in multiple-dose vials, should not be used for epidural or caudal anesthesia because safety has not been established with regard to intrathecal injection, either intentionally or unintentionally, of such preservatives.
It is essential that aspiration for blood or cerebrospinal fluid (where applicable) be done prior to injecting any local anesthetic, both the original dose and all subsequent doses, to avoid intravascular or subarachnoid injection. However, a negative aspiration does not ensure against an intravascular or subarachnoid injection.
Until further experience is gained in pediatric patients younger than 12 years, administration of Bupivacaine Hydrochloride in this age group is not recommended.
Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people. Single-dose ampoules and single-dose vials of Bupivacaine Hydrochloride without epinephrine do not contain sodium metabisulfite.

PRECAUTIONS

General: 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.
During major regional nerve blocks, the patient should have IV fluids running via an indwelling catheter to assure a functioning intravenous pathway. The lowest dosage of local anesthetic that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should be used when feasible.
Epidural Anesthesia: During epidural administration of Bupivacaine Hydrochloride, 0.5% solutions should be administered in incremental doses of 3 mL to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Injections should be made slowly, with frequent aspirations before and during the injection to avoid intravascular injection. Syringe aspirations should also be performed before and during each supplemental injection in continuous (intermittent) catheter techniques. An intravascular injection is still possible even if aspirations for blood are negative.
During the administration of epidural anesthesia, it is recommended that a test dose be administered initially and the effects monitored before the full dose is given. When using a "continuous" catheter technique, test doses should be given prior to both the original and all reinforcing doses, because plastic tubing in the epidural space can migrate into a blood vessel or through the dura. Following the test dose, the heart rate should be monitored for a heart rate increase.
Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with their age and physical status. Local anesthetics should also be used with caution in patients with hypotension or heartblock.
Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be performed after each local anesthetic injection. Local anesthetic solutions containing a vasoconstrictor should be used cautiously and in carefully restricted quantities in areas of the body supplied by end arteries or having otherwise compromised blood supply such as digits, nose, external ear, or penis. Patients with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result.
Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of potent inhalation anesthetics. 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.
The need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available.
Use in Head and Neck Area: Small doses of local anesthetics injected into the head and neck area, including retrobulbar, dental, 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. Patients receiving retrobullar 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.
Use in Ophthalmic Surgery: 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. 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.
Mixing Bupivacaine Hydrochloride with other local anesthetics is not recommended.
Clinically Significant Drug Interactions: The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants should generally be avoided. Concurrent administration of vasopressor drugs and of ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accidents.
Carcinogenesis, Mutagenesis, Impairment of Fertility: There is no evidence from human data that Bupivacaine Hydrochloride may be carcinogenic or mutagenic or that it impairs fertility.
Pregnancy Category C: Bupivacaine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. This does not exclude the use of Bupivacaine Hydrochloride at term for obstetrical anesthesia or analgesia.
Labor and Delivery: Bupivacaine Hydrochloride is contraindicated for obstetrical paracervical block anesthesia. Local anesthetics rapidly cross the placenta, and when used for epidural, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, fetal, 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. Epidural, caudal, or pudendal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts.
It is extremely important to avoid aortocaval compression by the gravid uterus during administration of regional block to parturients. To do this, the patient must be maintained in the left lateral decubitus position or a blanket roll or sandbag may be placed beneath the right hip and gravid uterus displaced to the left.
Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from bupivacaine, a decision should be made whether to discontinue nursing or not administer bupivacaine, taking into account the importance of the drug to the mother.
Pediatric Use: In pediatric patients younger than 12 years, administration of Bupivacaine Hydrochloride in this age group is not recommended.
Geriatric Use: This product is known to be sudstantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients.

ADVERSE REACTIONS

These adverse experiences are generally dose related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance, or from unintentional intravascular injection of the local anesthetic solution. 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. Also, hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia may occur. This may lead to secondary cardiac arrest if untreated.
Central Nervous System Reactions: These are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. Other central nervous system effects may be nausea, vomiting, chills, and constriction of the pupils. The incidence of convulsions associated with the use of local anesthetics varies with the procedure used and the total dose administered.
Cardiovascular System Reactions: High doses or unintentional intravascular injection may lead to high