SUMMARY OF PRODUCT CHARACTERISTICS

1. **Name of Drug Product:**

Name of the medicinal product
ANAWIN
Bupivacaine Injection B.P.

1.2 Strength :

100mg/20ml

2. **Qualitative and quantitative composition**

SR. NO.	PARTICULARS	GRADE	QTY/ML	FUNCTION
1.	Bupivacaine Hydrochloride	B.P.	5.0 mg	Active

For the excipients, refer 6.1

3. **Pharmaceutical dosage form**

Liquid Injection

4. **Clinical Particulars:**

4.1 Therapeutic indications:

Bupivacaine Injection is indicated for the production of local or regional anaesthesia or analgesia for surgery, dental and oral surgery, diagnostic procedures & therapeutic procedures, and for obstetrical procedures. Only the 0.25% and 0.5% concentration are indicated for intravenous regional anaesthesia.

The routes of administration & indicated bupivacaine concentrations are

Local infiltration	0.25%
Peripheral nerve block	0.25% and 0.5%
Sympathetic block	0.2%

4.2 Dosage and method of administration:

LOCAL ANAESTHETIC

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. Therapid 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 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 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.
The product should not be used for epidural anaesthesia and caudal anesthesia since it contains a preservative.
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 pf block	Conc.		Each dose	Motor Block
		(ml)	(mg)	
Local Infiltration	0.25%[2]	Up to max	Up to max	_
Peripheral nerves	0.5%[2]	5 to max	25 to max	Moderate to complete
	0.25%[2]	5 to max	12.5 to max	Moderate to complete
Sympathetic	0.25%[2]	20-50 ml	50-125 mg	

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 Solutions with or without epinephrine.

4.3 Contra-indications:

Bupivacaine Injection is contraindicated in obstetrical paracervical block anaesthesia. Its use in this technique has resulted in fetal bradycardia & death.
Bupivacaine is contraindicated in patients with a known hypersensitivity to it or to any local anaesthetic agents of the amide type or to other components of bupivacaine solutions.

4.4 Special warning and precautions for use:

Local anaesthetics should only be employed by clinicians who are well versed in diagnosis and 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, cardio pulmonary resuscitative equipment needed for proper management of toxic reactions & related emergencies. Delay in proper management of dose related toxicity under ventilation from any cause and for 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.
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 substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients.

4.5 Adverse Reactions

These adverse experiences are generally dose related and due to high plasma levels which may result from over dosage, 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 under ventilation 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 plasma levels and related depression of the myocardium, decreased

cardiac output, heart block, 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.

4.6 Pregnancy and lactation:

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4.7 Effects on ability to drive and use machines

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4.8 Overdoses:

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.

As per literature, 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.

5. Pharmacological properties:

5.1 Pharmacodynamic properties

Local anaesthetics block the generation & conduction of nerve impulses, presumably by increasing the threshold for electric excitation in the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anaesthesia is related to the diameter, myelination & conduction velocity of affected nerve fibres. Clinically order of loss of nerve function is as follows : i) pain ii) temperature iii) touch iv) proprioception v) Skeletal muscle tone.

Systemic absorption of local anaesthetic produces effects on the cardiovascular & central nervous system. At blood concentrations achieved with normal therapeutic doses, change in cardiac conduction, excitability, which may lead to AV block, ventricular arrhythmias & cardiac arrest. Contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output & arterial blood pressure.

Recent-clinical reports & animal research suggest that these cardiovascular changes are more likely to occur after unintended intravascular injection of bupivacaine.

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

5.2 Pharmacokinetic properties

The rate of systemic absorption of local anaesthetics is dependent upon the total dose & concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinepherine in anaesthetic solution. The onset of action of Bupivacaine is rapid and anaesthesia is long lasting. The duration of anaesthesia is significantly used local anaesthetic. 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.

Local anaesthetic appear to cross the placenta by passive diffusion. The rate & degree of diffussion is governed by

i) the degree of plasma protein binding
ii) the degree of ionization
iii) the degree of lipid solubility.

Fetal/maternal ratios of local anaesthetics appear to inversely related to the degree of ionization and lipid solubility of the drug. Lipid soluble, non-ionization drugs readily enter the fetal blood from the maternal circulation. Depending upon the route of administration, local anaesthetics 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.

Various pharmacokinetic parameters of the local anaesthetics 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 in adults is 2.7 hours & in neonates 8.1 hours.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium Chloride B.P.
Sodium Hydroxide B.P.
Methylparaben B.P.
Water for Injections B.P.

6.2 Shelf – life:

24 Months.

6.3 Special precautions for storage

Store below 30°C., protected from light.

6.4 Nature and contents of container:

20 ml Flint vial USP type-1 national vial stoppered with Grey Bromo Butyl Rubber Stopper & sealed with "NEON" Embossed Grey Lacquered Flip Off Aluminum Seal.

6.5 Special Precautions for Handling and Disposal:

Use as directed by a physician.

7. Marketing authorization holder:

M/s. NEON LABORATORIES LIMITED
140, Damji Shamji Industrial Complex,
28, Mahal Indl. Estate,
Mahakali Caves Road,
Andheri (East),
Mumbai - 400 093.

8. Marketing authorization number :

07631/07536/NMR/2019

9. Date of first authorization / Renewal of the authorization:

Date of first authorisation : 08/08/2022

10. Date of revision of the text:

July, 2023