SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product:

1.1 Product Name:
ANAWIN HEAVY
Bupivacaine Hydrochloride in Dextrose Injection USP

1.2 Strength (Composition):
20mg/4ml

1.3 Pharmaceutical dosage form:
Solution for Injection

2. Quality and Quantitative Composition:

2.1 Qualitative & Quantitative Declaration

SR. NO.	PARTICULARS	GRADE	QTY/ML	FUNCTION
1.	Bupivacaine Hydrochloride equivalent to anhydrous Bupivacaine Hydrochloride	USP	5.0 mg	Active
2.	Dextrose USP (Anhydrous)	USP	80.0 mg	Baricity adjustifier
3.	Sodium Hydroxide	USP	----	For pH adjustment
4.	Water for Injection (Bulk)	USP	q.s. to 1 ml	Vehicle

3. Pharmaceutical form:
A clear colourless solution

4. Clinical Particulars:

4.1 Therapeutic indications:

Bupivacaine Hydrochloride in Dextrose Injection USP is indicated for the production of subarachnoid block (spinal anesthesia). Standard textbooks should be consulted to determine the accepted procedures and techniques for the administration of spinal anesthesia.

4.2 Posology and method of 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 Spinal (Bupivacaine in Dextrose Injection, USP) should be reduced for elderly and debilitated patients and patients with cardiac and/or liver disease.

The extent and degree of spinal anesthesia depends upon several factors including dosage, specific gravity of the anesthetic solution, volume of solution used, force of injection, level of puncture, and position of the patient during and immediately after injection. 5 mg or 1.0 mL Bupivacaine Spinal has generally proven satisfactory for spinal anesthesia for lower extremity and perineal procedures including TURP and vaginal hysterectomy. Twelve mg (12 mg or 2.4mL) has been used for lower abdominal procedures such as abdominal hysterectomy, tubal ligation, and appendectomy. These doses are recommended as a guide for use in the average adult and may be reduced for elderly or debilitated patients. Because experience with Bupivacaine Spinal is limited in patients below the age of 18 years, dosage recommendations in this age group cannot be made.

Obstetrical Use: Doses as low as 6 mg bupivacaine hydrochloride have been used for vaginal delivery under spinal anesthesia. The dose range of 5 mg to 10.5 mg (1 mL to 2.1 mL) bupivacaine hydrochloride has been used for Cesarean section under spinal anesthesia.

In recommended doses, Bupivacaine Spinal produces complete motor and sensory block.

Unused portions of solutions should be discarded following initial use.

Bupivacaine Spinal should be inspected visually for discoloration and particulate matter prior to administration; solutions which are discolored or which contain particulate matter should not be administered.

4.3 Contra-indications:

Bupivacaine Spinal (Bupivacaine in Dextrose Injection, USP) is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amidetype.

The following conditions preclude the use of spinal anesthesia:

1. Severe hemorrhage, severe hypotension or shock and arrhythmias, such as complete heart block, which severely restrict cardiac output.
2. Local infection at the site of proposed lumbar puncture.
3. Septicemia.

4.4 Special warning and precautions for use:

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 DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST, AND, POSSIBLY, DEATH.

Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of glenohumeral 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. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. 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 chondrolysis; patients who experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

Spinal anesthetics should not be injected during uterine contractions, because spinal fluid current may carry the drug further cephalad than desired.

A free flow of cerebrospinal fluid during the performance of spinal anesthesia is indicative of entry into the subarachnoid space. However, aspiration should be performed before the anesthetic solution is injected to confirm entry into the subarachnoid space and to avoid intravascular injection.

Bupivacaine solutions containing epinephrine or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because a severe persistent hypertension may occur. Likewise, solutions of bupivacaine containing a vasoconstrictor, such as epinephrine, should be used with extreme caution in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe prolonged hypertension may result.

Until further experience is gained in patients younger than 18 years, administration of bupivacaine in this age group is not recommended.

Mixing or the prior or intercurrent use of any other local anesthetic with bupivacaine cannot be recommended because of insufficient data on the clinical use of such mixtures.

PRECAUTIONS

General:

The safety and effectiveness of spinal 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.

The patient should have I.V. 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.

Aspiration for blood should be performed before injection and injection should be made slowly. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients may require reduced doses. Reduced doses may also be indicated in patients with increased intra-abdominal pressure (including obstetrical patients), if otherwise suitable for spinal anesthesia.

There should be careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness after local anesthetic injection. Restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity. Spinal anesthetics should be used with caution in patients with severe disturbances of cardiac rhythm, shock, or heart block.

Sympathetic blockade occurring during spinal anesthesia may result in peripheral vasodilation and hypotension, the extent depending on the number of dermatomes blocked.

Blood pressure should, therefore, be carefully monitored especially in the early phases of anesthesia.

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 agents. 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 following conditions may preclude the use of spinal anesthesia, depending upon the physician's evaluation of the situation and ability to deal with the complications or complaints which may occur:

♦ Pre-existing diseases of the central nervous system, such as those attributable to pernicious anemia,poliomyelitis, syphilis, or tumor.

♦ Hematological disorders predisposing to coagulopathies or patients on anticoagulant therapy. Trauma to a blood vessel during the conduct of spinal anesthesia may, in some instances, result in uncontrollable central nervous system hemorrhage or soft tissue hemorrhage.

♦ Chronic backache and preoperative headache.

♦ Hypotension and hypertension.

♦ Technical problems (persistent paresthesias, persistent bloody tap).

♦ Arthritis or spinal deformity.

♦ Extremes of age.

♦ Psychosis or other causes of poor cooperation by the patient.

4.5 Interaction with other medicinal products and other forms of interaction:

Bupivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, e.g. certain anti-arrhythmics, such as lidocaine and mexiletine, since the systemic toxic effects are additive.

Specific interaction studies with bupivacaine and anti-arrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution is advised

4.6 Fertility, pregnancy and lactation

Pregnancy Category C :

With reference to literature 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 230 and 130 times respectively the maximum recommended human spinal dose. There are no adequate and well-controlled studies in

pregnant women of the effect of bupivacaine on the developing fetus. 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 Spinal at term for obstetrical anesthesia.

Labor and Delivery:

Spinal anesthesia has a recognized use during labor and delivery. Bupivacaine hydrochloride, when administered properly, via the epidural route in doses 10 to 12 times the amount used in spinal anesthesia has been used for obstetrical analgesia and anesthesia without evidence of adverse effects on the fetus. Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously and electronic fetal monitoring is highly advisable.

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 the gravid uterus displaced to the left.

Spinal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Spinal anesthesia has also been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. The use of obstetrical anesthesia may increase the need for forceps assistance.

Nursing Mothers:

It is not known whether local anesthetic drugs are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when local anesthetic drugs are administered to a nursing woman.

4.7 Effects on ability to drive and use machines:

Besides the direct anaesthetic effect, local anaesthetics may have a very mild effect on mental function and co-ordination even in the absence of overt toxicity and may temporarily impair locomotion and alertness.

4.8 Undesirable effects:

Reactions to bupivacaine are characteristic of those associated with other amide-type local anesthetics. The most commonly encountered acute adverse experiences which demand immediate countermeasures following the administration of spinal anesthesia are hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia. These may lead to cardiac arrest if untreated. In addition, dose-related convulsions and cardiovascular collapse may result from diminished tolerance, rapid absorption from the injection site or from unintentional intravascular injection of a local anesthetic solution. Factors influencing plasma protein binding, such as acidosis, systemic diseases which alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance.

Respiratory System: Respiratory paralysis or underventilation may be noted as a result of upward extension of the level of spinal anesthesia and may lead to secondary hypoxic cardiac arrest if untreated. Preanesthetic medication, intraoperative analgesics and sedatives, as well as surgical manipulation, may contribute to underventilation.

This will usually be noted within minutes of the injection of spinal anesthetic solution, but because of differing surgical maximal onset times, differing intercurrent drug usage and differing manipulation, it may occur at any time during surgery or the immediate recovery period.

Cardiovascular System: Hypotension due to loss of sympathetic tone is a commonly encountered extension of the clinical pharmacology of spinal anesthesia. This is more commonly observed in patients with shrunkenblood volume, shrunken interstitial fluid volume, cephalad spread of the local anesthetic, and/or mechanical obstruction of venous return. Nausea and vomiting are frequently associated with hypotensive episodes following the administration of spinal anesthesia. High doses, or inadvertent intravascular injection, may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, bradycardia, heart block, ventricular arrhythmias, and, possibly, cardiac arrest.

Central Nervous System: Respiratory paralysis or underventilation secondary to cephalad spread of the level of spinal anesthesia and hypotension for the same reason are the two most commonly encountered central nervous system-related adverse observations which demand immediate countermeasures.

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. Many of these effects may be related to local anesthetic techniques, with or without a contribution from the drug.

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

Allergic: Allergic-type reactions are rare and may occur as a result of sensitivity to the local anesthetic. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and, possibly, anaphylactoid-like symptomatology (including severe hypotension). Cross sensitivity among members of the amide-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitely established.

Other: Nausea and vomiting may occur during spinal anesthesia.

4. 9 Overdose:

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use or to underventilation (and perhaps apnea) secondary to upward extension of spinal anesthesia. Hypotension is commonly encountered during the conduct of spinal anesthesia due to relaxation of sympathetic tone, and sometimes, contributory mechanical obstruction of venous return.

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. At the first sign of change, oxygen should be administered.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group (ATC code): N01BB51

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.

5.2 Pharmacokinetic properties

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. A dilute concentration of epinephrine (1:200,000 or 5 mcg/mL) usually reduces the rate of absorption and peak plasma concentration of bupivacaine, permitting the use of moderately larger total doses and sometimes prolonging the duration of action.

The onset of action with bupivacaine is rapid and anesthesia is long-lasting. The duration of anesthesia is significantly longer with bupivacaine than with any other commonly used local anesthetic. 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 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 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.

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 in adults is 3.5 ± 2 hours and in neonates 8.1 hours.

5.3 Preclinical Safety Data:

Bupivacaine hydrochloride is a well-established active ingredient.

6.0 Pharmaceutical particulars:

6.1 List of excipients:

1. Dextrose USP (Anhydrous)
2. Sodium Hydroxide USP
3. Water for injection USP

6.2 Incompatibilities:
Not applicable.

6.3 Shelf – life:
18months

6.4 Special precautions for storage:
Store below 30°C., protected from light. Do not freeze

6.5 Nature and contents of container:
4mL Flint Ampoule with Black dotted 'Snap off' OPC. Such 5 ampoules are packed in a blister pack each such blister is then packed in a carton along with package insert

6.6 Special precautions for disposal and other handling:
The solution should be used immediately after opening of the ampoule. Any remaining solution should be discarded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7.0 Marketing Authorisation Holder:
NEON LABORATORIES LIMITED
140, Damji Shamji Industrial Complex,
28, Mahal Indl. Estate,
Mahakali Caves Road,
Andheri (East),
Mumbai - 400 093.

8.0 Marketing Authorization Number:

9.0 Date of First Authorization /Renewal of the Authorization:
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10. Date of Revision of the Text:
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11 Dosimetry (If Applicable)
Not Applicable

12 Instructions for preparation of Radiopharmaceuticals (If Applicable)
Not Applicable