1.3.1 Summary of Product Characteristics (SmPC)

1. Name of Medicinal Product

VENCHURA BUPIVACAINE INJECTION

BUPIVACAINE HYDROCHLORIDE IN DEXTROSE INJECTION USP 5MG/ML

2. Qualitative and Quantitative Composition

2.1. Qualitative declaration:

Composition of the Drug product:

Each ml contains

Bupivacaine hydrochloride USP

Eq. to Anhydrous Bupivacaine hydrochloride 5 mg

Dextrose Monohydrate USP 80 mg

Water for Injection USP Q.S.

Qualitative & Quantitative Composition Formula:

Batch size: 570 Liters

Sr. No.	Name of raw material	Specification	Label claim	% Overages	Qty per ml with Overages (mg)	Quantity / Batch	Function
1.	Bupivacaine hydrochloride Eq. to Anhydrous Bupivacaine hydrochloride	USP	5mg	Nil	5 mg	*3.003 kg	Local anaesthetic
2.	Dextrose (Monohydrate)	USP	80 mg	Nil	80 mg	45.600 Kg	For tonicity adjustment
3.	Water for Injection	USP	---	Nil	Q.S.	Q.S.	Vehicle

* This quantity may vary according to the final assay as is basis.

Calculations:

Calculate the quantity of ingredient as per the required batch size.

$$= \frac{\text{Label claim x Batch Size x 100}}{\text{\% Assay as is basis}}$$

Note: If Assay is more than 100 %, consider it as 100%. If assay is less than 100 % then consider actual Assay Value.

3. Pharmaceutical form

LIQUID INJECTION

A Clear, Colourless, aqueous Solution

4. Clinical particulars

4.1 Therapeutic indications

Bupivacaine Hydrochloride with Dextrose Injection USP is indicated for: It is indicated in adults and children of all ages for intrathecal (subarachnoid) spinal anaesthesia for surgery (urological and lower limb surgery lasting 2 - 3 hours, abdominal surgery lasting 45 - 60 minutes).

4.2 Posology and method of administration

Bupivacaine Hydrochloride with Dextrose Injection USP should only be used by clinicians with experience of regional anaesthesia or under their supervision. The lowest possible dose for adequate anaesthesia should be used. The doses given below are guides for adults and the dosage should be adjusted to the individual patients.

Adults and children above 12 years of age

The doses recommended below should be regarded as a guide for use in the average adult. The figures reflect the expected average dose range needed. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

Dosage recommendations

Intrathecal anaesthesia for surgery:

2 - 4 ml (10 - 20 mg Bupivacaine Hydrochloride).

The dose should be reduced in elderly patients and patients in late stages of pregnancy.

Neonates, infants and children up to 40 kg

Bupivacaine Hydrochloride with Dextrose Injection USP may be used in children. One of the differences between small children and adults is a relatively high CSF volume in infants and neonates, requiring a relatively larger dose/kg to produce the same level of blocks as compared to adults.

Paediatric regional anaesthesia procedures should be performed by qualified clinicians who are familiar with this population and the techniques. The doses in the table should be regarded as guidelines for use in paediatric patients. Individual variations occur. Standard textbooks should be consulted for factors affecting specific block technique and for individual patient requirements. The lowest dose required for adequate should be used.

Dosage recommendations in neonates, infants and children

Body weight (kg)	Dose (mg/kg)
< 5	0.40 - 0.50 mg/kg
5 to 15	0.30 - 0.40 mg/kg
15 to 40	0.25 - 0.30 mg /kg

The spread of anaesthesia obtained with Bupivacaine Hydrochloride with Dextrose Injection USP depends on several factors including the volume of solution and the position of the patient during and following the injection. When injected at the L3 – L4 intevertebral space, with the patients in the sitting position, 3 ml of Bupivacaine Hydrochloride with Dextrose Injection USP to the T7 – T10 spinal segments. With the patient receiving the injection in the horizontal position and then turned supine, the blockade spreads to T4 – T7 spinal segments. It should be understood that the level of spinal anaesthesia archived with any local anaesthetic can be unpredictable in a given patient.

The recommended site of injection is below L3. The effects of injections of Bupivacaine Hydrochloride with Dextrose Injection USP exceeding 4 ml have not yet been studied and such volumes can therefore not be recommended.

4.3 Contraindications

The Product is contraindicated in the following situations:

Hypersensitivity to local anaesthetics of the amide type or to any of the excipients.

Intrathecal anaesthesia, regardless of the local anaesthetic used, has its own contraindications, which include:

• Active disease of the central nervous system such as meningitis, poliomyelitis, intracranial haemorrhage, sub - acute combined degeneration of the cord due to pernicious anaemia and cerebral and spinal tumours.

• Spinal stenosis and active disease (e.g. spondylitis, tuberculosis, tumour) or recent trauma (e.g. fracture) in the vertebral column.

• Septicaemia.

• Pyogenic infection of the skin at or adjacent to the site of lumbar puncture.

• Cardiogenic or hypovolaemic shock.

• Coagulation disorders or ongoing anticoagulation treatment.

4.4 Special warnings and precautions for use

General

Intrathecal anaesthesia should only be undertaken by clinicians with the necessary knowledge and experience. Regional anaesthetic procedures should always be performed in a properly equipped and staffed area. Resuscitative equipment and drugs should be immediately available and the anaesthetist should remain in constant attendance.

Intravenous access, e.g. an i.v. infusion, should be in place before starting the intrathecal anaesthesia. The clinician responsible should take the necessary precautions to avoid intravascular injection and be appropriately trained and familiar with the diagnosis and treatment of side effects, systemic toxicity and other complications. If signs of acute systemic toxicity or total spinal block appear, injection of the local anaesthetic should be stopped immediately.

Like all local anaesthetic drugs, Bupivacaine hydrochloride may cause acute toxicity effects on the central nervous and cardiovascular systems, if utilised for local anaesthetic procedures resulting in high blood concentrations of the drug. This is especially the case after unintentional intravascular administration or injection into highly vascular areas.

Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported in connection with high systemic concentrations of Bupivacaine. Should cardiac arrest occur, a successful outcome may require prolonged resuscitative efforts. High systemic concentrations are not expected with doses normally used for intrathecal anaesthesia.

There is an increased risk of high or total spinal blockade, resulting in cardiovascular and respiratory depression, in the elderly and in patients in the late stages of pregnancy. The dose should therefore be reduced in these patients.

Intrathecal anaesthesia with any local anaesthetic can cause hypotension and bradycardia which should be anticipated and appropriate precautions taken. These may include preloading the circulation with crystalloid or colloid solution. If hypotension develops it should be treated with a vasopressor such as ephedrine 10-15 mg intravenously. Severe hypotension may result from hypovolaemia due to haemorrhage or dehydration, or aortocaval occlusion in patients with massive ascites, large abdominal tumours or late pregnancy. Marked hypotension should be avoided in patients with cardiac decompensation.

Patients with hypovolaemia due to any cause can develop sudden and severe hypotension during intrathecal anaesthesia

Intrathecal anaesthesia can cause intercostal paralysis and patients with pleural effusions may suffer respiratory embarrassment. Septicaemia can increase the risk of intraspinal abscess formation in the postoperative period.

Neurological injury is a rare consequence of intrathecal anaesthesia and may result in paraesthesia, anaesthesia, motor weakness and paralysis. Occasionally these are permanent.

Before treatment is instituted, consideration should be taken if the benefits outweigh the possible risks for the patient.

Patients in poor general condition due to ageing or other compromising factors such as partial or complete heart conduction block, advanced liver or renal dysfunction require special attention, although regional anaesthesia may be the optimal choice for surgery in these patients.

Patients treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be kept under close surveillance and ECG monitoring considered, since cardiac effects may be additive.

4.5 Interaction with other medicinal products and other forms of interaction

Bupivacaine hydrochloride should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, e.g. certain antiarrhythmics, 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 Use in Pregnancy and lactation

Pregnancy

There is no evidence of untoward effects in human pregnancy. In large doses, there is evidence of decreased pup survival in rats and an embryological effect in rabbits if Bupivacaine hydrochloride is administered in pregnancy. Bupivacaine Hydrochloride with Dextrose Injection USP should not therefore be given in early pregnancy unless the benefits are considered to outweigh the risks. It should be noted that the dose should be reduced in patients in the late stages of pregnancy.

Breast-feeding

Bupivacaine hydrochloride passes into breast milk, but the risk of this affecting the child appears unlikely with therapeutic doses.

4.7 Effects on ability to drive and use machines

Depending on the dose and method of administration, Bupivacaine hydrochloride can have a transient effect on movement and coordination.

4.8 Undesirable effects

The adverse reaction profile for Bupivacaine Hydrochloride with Dextrose Injection USP is similar to those for other long acting local anaesthetics used for intrathecal anaesthesia.

Frequency categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from available data).

Systemic: extensive topical use of corticosteroids may lead to systemic side effects*.

* See Section 4.4 for further information.

Very common (>1/10)	General: Nausea Cardiac disorder: Hypotension, bradycardia
Common (>1/100)	CNS: Post lumbar puncture headache GI: Vomiting Genitourinary: Urinary retention, urinary incontinence

Uncommon (1/100 – 1/1000)	CNS: Paraesthesia, paresia, dysaesthesia Musculoskeletal: Muscle weakness, back pain
Rare (<1/1000)	Cardiac: Cardiac arrest General: Allergic reactions, anaphylactic shock CNS: Accidental total spinal blockade, paraplegia, paralysis, neuropathy, arachnoiditis Airways: Respiratory depression

4.9 Overdose

Bupivacaine Hydrochloride with Dextrose Injection USP used as recommended, is not likely to cause blood levels high enough to cause systemic toxicity. However, if other local anaesthetics are concomitantly administered, toxic effects are additive and may cause systemic toxic reactions.

Acute systemic toxicity

Systemic toxicity is rarely associated with spinal anaesthesia but might occur after accidental intravascular injection. Systemic adverse reactions are characterised by numbness of the tongue, light-headedness, dizziness and tremors, followed by convulsions and cardiovascular disorders.

Treatment of acute systemic toxicity

No treatment is required for milder symptoms of systemic toxicity but if convulsions occur then it is important to ensure adequate oxygenation and to arrest the convulsions if they last more than 15–30 seconds. Oxygen should be given by face mask and the respiration assisted or controlled if necessary. Convulsions can be arrested by injection of thiopental 100–150 mg intravenously or with diazepam 5-10 mg intravenously. Alternatively, succinylcholine 50-100 mg intravenously may be given but only if the clinician has the ability to perform endotracheal intubation and to manage a totally paralysed patient.

High or total spinal blockade causing respiratory paralysis should be treated by ensuring and maintaining a patent airway and giving oxygen by assisted or controlled ventilation.

Hypotension should be treated by the use of vasopressors, e.g. ephedrine 10-15 mg intravenously and repeated until the desired level of arterial pressure is reached. Intravenous fluids, both electrolytes and colloids, given rapidly can also reverse hypotension.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bupivacaine Hydrochloride is an Anaesthetic & Dextrose for tonicity adjustment

ATC code: N01BB01

Bupivacaine hydrochloride is a long-acting local anaesthetic of the amide type. Bupivacaine hydrochloride reversibly blocks impulse conduction in the nerves by inhibiting the transport of sodium ions through the nerve membrane. Similar effects can also be seen on excitatory membranes in the brain and myocardium.

Bupivacaine Hydrochloride with Dextrose Injection USP is intended for hyperbaric spinal anaesthesia. The relative density of the solution for injection is 1.026 at 20ºC (equivalent to 1.021 at 37 ºC) and the initial distribution into the subarachnoid space is markedly influenced by gravity. For administration into the spine, a small dose is given, which gives a relatively low concentration and short duration of effect, Bupivacaine (without glucose) produced a less predictable block but with a longer duration of effect than Bupivacaine hydrochloride (with glucose).

5.2 Pharmacokinetic properties

Absorption:

The plasma concentration of local anaesthetics is dependent upon the dose, the route of administration, the patient's hemodynamic/circulatory condition, and the vascularity of the injection site. The addition of epinephrine to bupivacaine may decrease the peak plasma concentration, whereas the time to peak plasma concentration usually is little affected. The effect varies with the type of block, dose and concentration.

Following injection of bupivacaine 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 gradual decline to insignificant levels during the next three to six hours. Intercostal blocks give the highest peak plasma concentration due to a rapid absorption (maximum plasma concentrations in the order of 1-4 mg/L after a 400 mg dose), while subcutaneous abdominal injections give the lowest plasma concentration. Epidural and major plexus blocks are intermediate. In children, rapid absorption

and high plasma concentrations (in the order of 1-1.5 mg/L after a dose of 3 mg/kg) are seen with caudal block.

Bupivacaine shows complete, biphasic absorption from the epidural space with plasma half-lives in the order of seven minutes after initial administration, slowing to six hours over time. The slow absorption is rate-limiting in the elimination of bupivacaine, which explains why the apparent elimination half-life after epidural administration is longer than after intravenous administration.

Distribution:

Local anesthetics are bound to plasma proteins in varying degrees. The highly lipophilic agents, such as bupivacaine, are far more highly protein-bound than the more hydrophilic compounds. Bupivacaine is approximately 95% protein-bound in normal adults. Generally, the lower the plasma concentration of drug, the higher the percentage of drug bound to plasma proteins. If plasma protein concentrations are decreased, more of the free drug will be available to exert activity. Bupivacaine is mainly bound to alpha-1-acid glycoprotein.

Bupivacaine readily crosses the placenta and equilibrium in regard to the unbound concentration is rapidly reached. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization and (3) the degree of lipid solubility. The degree of plasma protein binding in the foetus is less than in the mother, which results in lower total plasma concentrations in the foetus than in the mother. The free concentration, however, is the same in both mother and foetus.

Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding because only the free, unbound drug is available for placental transfer. Bupivacaine with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4).

Bupivacaine has a total plasma clearance of 0.58 L/min a volume of distribution at steady state of 73 L.

An increase in total plasma concentration has been observed during continuous epidural infusion for postoperative pain relief. This is related to a postoperative increase in alpha-1-acid glycoprotein. The unbound, i.e. pharmacologically active, concentration is similar before and after surgery.

Metabolism:

Because of its amide structure, bupivacaine is extensively metabolized in the liver predominantly by aromatic hydroxylation to 4-hydroxy-bupivacaine and N-dealkylation to 2,6- pipecoloxylidine (PPX), both mediated by cytochrome P450 3A4. The major metabolite of bupivacaine is pipecoloxylidine, a dealkylated derivative. Patients with hepatic disease may be more susceptible to the potential toxicities of the amide-type local anesthetics.

Excretion:

The plasma elimination half-life of bupivacaine in adults is 2.7 hours (range 1.2 to 4.6 hours). In infants, the half-life ranges from 6 to 22 hours, thus it is significantly longer than in adults. Half-life is also prolonged in the elderly. Bupivacaine has an intermediate hepatic extraction ratio of 0.38 after i.v. administration. In children between 1 to 7 years the pharmacokinetics are similar to those in adults.

The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by renal perfusion and factors affecting urinary pH.

Clearance of bupivacaine is almost entirely due to liver metabolism and more sensitive to changes in intrinsic hepatic enzyme function than to liver perfusion.

5.3 Preclinical safety data

No Data available

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sr. No.	Ingredients Name	Specification
1.	Dextrose (Monohydrate)	USP
2.	Water for Injection	USP

6.2 Incompatibilities: In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products

6.3 Shelf-life: 36 Months

6.4 Special precautions for storage:

Store below 30°C. Protect from light.

6.5 Nature and contents of container:

BUPIVACAINE HYDROCHLORIDE IN DEXTROSE INJECTION USP 5MG/ML

A Clear colourless Solution is filled and sealed in 4 ml Amber Ampoule yellow Ring Snap off Ampoule. 5 such ampoules are packed in a carton along with leaflet.

6.6 Special precautions for disposal and other handling

Not Applicable

7-Marketing Authorization Holder:

VENCHURA PHARMACEUTICALS LIMITED.,

5, Mercy Eneli Street, Surulere,

Lagos, Nigeria.

8- Marketing Authorization Number (s):

Product license / registration Number (s)

9- Manufacturer Name:

FARBE FIRMA PVT. LTD.
Plot no.1508, GIDC Estate, Ankleshwar-393 002,
Dist-Bharuch, Gujarat, India.

10- Date of first authorization/renewal of the authorization:

11- Date of revision of the text:
