1.3.1 SUMMARY PRODUCT CHARACTERISTICS (SmPC)

<table>
<tr><td>1</td><td>Name of the Finished Medicinal Product:</td></tr>
<tr><td>1.1</td><td>Product Name:
Bupivacaine Hydrochloride with Dextrose Injection USP</td></tr>
<tr><td>1.2</td><td>Strength : 5 mg/ml</td></tr>
<tr><td>1.3</td><td>Pharmaceutical Form: Injection</td></tr>
<tr><td>2</td><td>Qualitative and Quantitative Compositions:</td></tr>
<tr><td></td><td>Qualitative Declaration:
Active component
INN Name: Bupivacaine Hydrochloride
Quantitative Declaration:
Each ml contains
Bupivacaine Hydrochloride BP
Equivalent to Anhydrous Bupivacaine Hydrochloride…...5.0 mg.
Dextrose Anhydrous USP……..…80 mg.
Water for Injection BP…….q.s

<table>
<tr><th>Sr. No.</th><th>Content Name</th><th>Quality Standard</th><th>Quantity in mg /ml</th></tr>
<tr><td>1</td><td>Bupivacaine Hydrochloride equivalent to Anhydrous Bupivacaine Hydrochloride</td><td>BP</td><td>5.1 mg*</td></tr>
<tr><td>2</td><td>Dextrose Anhydrous</td><td>USP NF</td><td>81.6 mg*</td></tr>
<tr><td>3</td><td>Sodium Hydroxide</td><td>BP</td><td>q.s. #</td></tr>
<tr><td>4</td><td>Hydrochloric Acid</td><td>BP</td><td>q.s. #</td></tr>
<tr><td>5</td><td>Water for Injection</td><td>BP</td><td>q.s to 1.0 ml</td></tr>
</table>
* 2% overages added
# For pH adjustment only.
BP: British Pharmacopoeia.
USP NF: United States Pharmacopoeia National Formulary</td></tr>
<tr><td>3</td><td>Pharmaceutical form: Injection
Description: A clear, colourless solution</td></tr>
</table>

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 $L_3 – L_4$ intevertebral space, with the patients in the sitting position, 3 ml of Bupivacaine Hydrochloride with Dextrose Injection USP to the $T_7 – T_{10}$ spinal segments. With the patient receiving the injection in the horizontal position and then turned supine, the blockade spreads to $T_4 – T_7$ 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 L_3. 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	**Contra-indications:** 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 aorto-caval 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 drugs, other forms of interactions:** 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 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	**Usage in pregnancy& 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. **Lactation:** 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 operate machine:** 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.

		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 (</1000)	Cardiac: Cardiac arrest General: Allergic reactions, anaphylactic shock CNS: Accidental total spinal blockade, paraplegia, paralysis, neuropathy, arachnoiditis Airways: Respiratory depression

4.9 **Overdose and special antidotes :**

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 (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:** Bupivacaine hydrochloride is very liposoluble with an oil/water distribution coefficient of 27.5. Bupivacaine hydrochloride hydrochloride displays complete and bi-phasic absorption from the subarachnoid space, with half-lives for the two phases of approx. 50 and approx. 400 minutes, with large variations. The slow absorption phase is the rate-determining factor in the elimination of Bupivacaine hydrochloride, which explains why the apparent half-life is longer than after the intravenous administration. Absorption from the subarachnoid space is relatively slow, which, in combination with the low dose required for spinal anaesthesia, gives a relatively low plasma concentration (approx. 0.4 mg/ml per 100 mg injected). Bupivacaine hydrochloride is metabolized almost completely in the liver, predominantly through aromatic hydroxylation to 4-hydroxybupivacaine and N-dealkylation to PPX, both of which are mediated by cytochrome P450 3A4. Clearance is thus dependent on hepatic perfusion and the activity of the metabolizing enzyme. • Rapid onset of action and long duration i.e. T_{10} –T_{12} segments – duration 2–3 hours. • Muscular relaxation of lower extremities lasts 2–2.5 hours. • Blockade of the abdominal muscles lasts 45–60 minutes. The duration of motor blockade does not exceed duration of analgesia. In children the pharmacokinetics are similar to that in adults. Bupivacaine hydrochloride crosses the placenta and the concentration of free Bupivacaine is the same in the mother and the foetus. However, the total plasma concentration is lower in the foetus, which has a lower degree of protein binding.
6	**Pharmaceutical Particulars:**
6.1	**List of excipients:** Dextrose Anhydrous USP NF Sodium Hydroxide BP Hydrochloric Acid BP Water for Injection BP
6.2	**Incompatibilities:** In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products
6.3	**Shelf life:** 24 Months
6.4	**Special precautions for storage:** Store below 30°C. Protect from light.
6.5	**Nature and contents of container:** Bupivacaine Hydrochloride with Dextrose Injection USP is available in 4 ml sterile ampoule (5 ml USP Type I, clear glass ampoule with green ring). 5 such ampoules are available in a blister pack, packed in a carton along with pack insert.
6.6	**Special precaution for disposal :** Not Applicable
7	**Registrant:** **Marketing Authorization Holder:** **M/s PHILLIPS PHARMACEUTICALS (NIGERIA) LTD.** Address : Afprint Industrial Estate, Plot 122-132,

	Apapa Oshodi Expressway Lagos Country : Nigeria. Telephone : +234 806761764 Fax : --- E-mail : --- **Manufacturing Site Address:** **M/s THEMIS MEDICARE LIMITED** Sector 6A, Plot No. 16, 17 & 18, IIE, SIDCUL, Haridwar – 249 403, Uttarakhand, INDIA. Telephone: 91-1334-239321/22 Fax: 91-334-239217 E-mail: hwdgmtech@themismedicare.com
8	**Date of Revision of the Text:** Not Applicable
9	**Dosimetry (if applicable):** Not Applicable
10	**Instruction for preparations of Radiopharmaceutical (if applicable):** Not Applicable