Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Bupivacaine Hydrochloride USP(anhydrous) and Dextrose BP

2. Qualitative and quantitative composition
Each 4 ml contains 20 mg of bupivacaine hydrochloride anhydrous USP and 320 mg Dextrose BP.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
IV injection

4. Clinical particulars

4.1 Therapeutic indications
Bupivacaine Heavy is indicated in adults and children of all ages for intrathecal spinal anaesthesia
For urological or lower limbs surgery, including hip surgery lasting 1.5 to 3 hours
For lower abdominal surgery (including caesarean section) lasting 1.5 to 3 hours

4.2 Posology and method of administration
The clinician's experience and knowledge of the patient's physical status are of importance in calculating the required dose. The lowest dose required for adequate anaesthesia should be used. Individual variations in onset and duration occur, and the extent of the spread of anaesthesia may be difficult to predict, but will be affected by the volume of the drug used, especially with the isobaric (plain) solution. The doses recommended below should be regarded as a guide for use in the average adult Spinal anaesthesia for surgery: 2-4 ml (10-20 mg Bupivacaine hydrochloride).
The spread of anaesthesia obtained with Bupivacaine depends on several factors including the volume of the solutions and the position if the patients during and following the injection.
When injected in the L3-L4 intervertebral space with the patient in the sitting position, 3 ml of Bupivacaine spreads to the T7- T10 spinal segments.
With the patient receiving the injection in the horizontal position and then turned supine, the blockade spine spreads to T4-T7 spinal segments. It should be understood that the level of spinal anaesthetic can be unpredictable in a given patient

The dose should be reduced in the elderly and in patients in the late stages of pregnancy (see section 4.4).

4.3 Contraindications

Bupivacaine (Bupivacaine in Dextrose Injection, USP) is contraindicated in patients with a known hypersensitivity to it or to any local anaesthetic agent of the amide-type.

General contraindications related to intrathecal anaesthesia should be taken into account:

- Acute active diseases of the cerebrospinal system such as meningitis, tumours, poliomyelitis and cranial haemorrhage.
- Spinal stenosis and active disease (e.g. spondylitis, tuberculosis, tumour) or recent trauma (e.g. facture) in the vertebral column.
- Septicaemia.
- Pernicious anaemia with subacute combined degeneration of the spinal cord.
- Pyogenic infection of the skin at or adjacent to the site of puncture.
- Cardiogenic or hypovolaemic shock.
- Coagulation disorders or ongoing anti-coagulation treatment.

4.4 Special warnings and precautions for use

Bupivacaine should not be injected into inflamed or infected areas.

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, see sections 4.8 & 4.9).

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. (See section 4.5)

Like all local anaesthetic drugs, bupivacaine 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.

An uncommon but dangerous side effect in spinal anaesthesia is extensive or total spinal blockade, which results in cardiovascular depression and respiratory depression.

The cardiovascular depression is caused by sympathetic blockade, which can result in hypotension and bradycardia, or even cardiac arrest.

Respiratory depression can be caused by blockade of the innervation of the respiratory muscles, including the diaphragm.

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.

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

Neurological disorders, such as multiple sclerosis, hemiplegia, paraplegia and neuromuscular disturbances are not thought to be adversely affected by intrathecal anaesthesia, but caution should be exercised.

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

Intrathecal anaesthesia with any local anaesthetic can cause hypotension and bradycardia which should be anticipated and appropriate precautions taken. Vasopressors should be used routinely and preferably prophylactically. It is recommended that alpha-agonist drugs are the most appropriate agents. Furthermore, I.V. colloid preloading or crystalloid co-loading should be used in addition to vasopressors. Severe hypotension may result from hypovolaemia due to haemorrhage or dehydration, or aorto-caval occlusion in patients with massive ascites, large abdominal tumours or large uterus in the late stage of pregnancy. Hypotension due to hypovolemia should be treated with intravenous fluid therapy according to current guidelines. Marked hypotension should be avoided in patients with cardiac decompensation or cerebrovascular disease.

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.

If the sue of regional analgesia is indicated for patients with angina pectoris or previous myocardial infarction, epidural analgesia is often preferred where severe hypotension can be more easily counteracted due to the longer duration of the attack. Alternatively, spinal analgesia can be administered via a subarachnoid catheter which allows for a gradual accumulation of analgesia Before treatment is instituted, consideration should be taken if the benefits outweigh the possible risks for the patient.

This medicinal product contains less than 1 mmol of sodium (23 mg) per ampoule, That is to say essentially “sodium-free”.

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 drugs that are structurally similar to amide-type local anaesthetics, i.e. anti-arrhythmic drugs such as lidocaine, mexiletine and tocainide, as the toxic effects are additive.

Cimetidine reduces the clearance of bupivacaine with a reduction in dosage as a possible consequence.

Using bupivacaine and verapamil at the same time may result in an increased risk of a heart blockage.

Using bupivacaine and propofol at the same time may increase the hypnotic effect of the propofol.

Using bupivacaine and ACE inhibitors at the same time may result in bradycardia and hypotension with impairment of consciousness as a consequence.

No specific interaction studies with bupivacaine and class III antiarrhythmic drugs have been carried out, but caution is recommended (See also section 4.4).

4.6 Pregnancy and Lactation

Pregnancy

It is reasonable to assume that a large number of pregnant women and women of childbearing age have been given bupivacaine.

No specific disturbances to the reproductive process have so far been reported, e.g. no increased incidence of malformations (See also section 5.2. Pharmacokinetic properties).

However, note that the dose should be reduced by 20-30% for patients in the late stages of pregnancy due to the risk of neonatal respiratory depression, hypotension and bradycardia. (See also section 4.4).

Bupivacaine transfers across to the placenta. Although the concentration of bupivacaine in the umbilical cord are lower than in the mother´s serum concentrations, the free bupivacaine concentrations will remain the same.

Breast-feeding

Bupivacaine enters in the mother's milk, but such small quantities that there is generally no risk of affecting the child at therapeutic dose levels.

4.7 Effects on ability to drive and use machines

Bupivacaine has minor influence on the 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 CNS toxicity and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

The adverse reaction profile for Bupivacaine is similar to those for other long- acting local anaesthetics administered intrathecally.

Undesirable effects caused by the product per se are difficult to distinguish from the physiological effects of the nerve block (e.g. decrease in blood pressure, bradycardia, temporary urinary retention), events caused directly (e.g. spinal haematoma) or indirectly (e.g. meningitis, epidural abcess) by needle puncture or events associated to cerebrospinal leakage (e.g. postdural puncture headache).

System Organ Class	Very Common (>1/10)	Common (>1/100, <1/10)	Uncommon (>1/1,000, <1/100)	Rare (<1/1,000)
Cardiac disorders	Hypotension, bradycardia			Cardiac arrest
Gastrointestinal disorders	Nausea	Vomiting		
Nervous system disorders		Postdural puncture headache	Paraesthesia, paresis, dysaesthesia	Total spinal block (unintentional), paraplegia, paralysis, neuropathy, arachnoiditis
Renal and urinary disorders		Urinary retention, urinary incontinence		
Musculoskeletal, connective tissue and bone disorders			Muscle weakness, back pain	
Immune system disorders				Allergic reactions, anaphylactic shock
Respiratory disorders				Respiratory depression

Paediatric population

Adverse drug reactions in children are similar to those in adults, however, in children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during sedation or general anaesthesia

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Symptoms of overdosing are: Hypotension. Bradycardia. Arrhythmia. CNS problems.

Acute systemic toxicity:

Bupivacaine, 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.

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:

If indications of acute systemic toxicity or total spinal blockade appear, injection of the local anaesthetic must be discontinued immediately, and neurological symptoms (convulsions, CNS depression) must be treated immediately and adequate ventilation must be ensured (free airways, oxygen, intubation if needed and controlled ventilation)

If the circulatory system collapses, cardiopulmonary resuscitation must be started immediately. An optimal supply of oxygen, ventilation, stabilization of the circulatory system and treatment of acidosis are vitally important. Standard cardiac arrests drugs (e.g. adrenaline) should be given according to ALS guidelines. The use of intravenous 20% lipid emulsion should be considered. Cardiac arrest due to bupivacaine can be resistant to electrical defibrillation and resuscitation must be continued energetically for a prolonged period.

If cardiovascular depression (hypotension, bradycardia) occurs, a vasopressor (preferably with an inotropic effect) should be given, such as ephedrine 5-10 mg i.v. and if necessary this dosage should be repeated after 2-3 minutes. It may also be necessary to inject liquid intravenously. The ephedrine dosage for children should be adjusted according to height and weight.

If convulsions caused by systemic toxicity occur, the objective of treatment is to maintain the oxygen supply, stop the convulsions and ease the circulation. Oxygen should be given and ventilation via support (bag mask ventilation or tracheal intubation). If the convulsions attacks do not stop spontaneously within 15-20 seconds, an anti-convulsive treatment should be administered intravenously.

Prolonged cramping may endanger the patient´s breathing and oxygen supply. Endotracheal intubation should be considered in these cases.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Amide-type local anaesthetics, ATC code: CTD10374

Mechanism of action

Bupivacaine is a local anaesthetic of the amide type. Given as an intrathecal anaesthetic, bupivacaine has a rapid onset and a medium to long duration.

The duration is dose-dependent.

Like other anaesthetics, bupivacaine reversibly blocks impulse conduction in the nerves by inhibiting the transport of sodium ions through the nerve membrane.

Bupivacaine Heavy is hyperbaric and its initial spread in the intrathecal space is affected by gravity.

Due to the small dose, the intrathecal spread results in a relatively low concentration, and the duration of local anaesthesia tends to be relatively shorter.

5.2 Pharmacokinetic properties

Absorption and distribution

Bupivacaine has a pKa 8.2 and partition coefficient of 346 (25° C, n-octanol/phosphate buffer, pH 7.4). The metabolites possess pharmacological activity which is lower than that of bupivacaine. Bupivacaine displays complete and bi-phasic absorption from the subarachnoid space, with half- lives for the two phases of approx. 50 and approx. 408 minutes. The slow absorption phase is the rate-determining factor in the elimination of bupivacaine, which explains why the apparent half-life is longer than after the intravenous administration. The concentration of bupivacaine in plasma after intrathecal block is low compared with those following other regional anaesthesia procedures due to the low dose required for intrathecal anaesthesia. Generally, the maximum plasma concentration increase is approximately 0.4 mg/l for every 100 mg injected. This means that a 20 mg dose would result in plasma levels of 0.1 mg/l.

Biotransformation

After intravenous administration, bupivacaine has a total plasma clearance of 0.58 l/min, a volume of distribution at steady state of 73 l, an elimination half- life of 2.7 hours and an intermediate hepatic extraction ratio of 0.38. In plasma, bupivacaine is associated with α1-acid glycoprotein, with 96% bonding with plasma. Clearance of bupivacaine is almost entirely due to liver metabolism, and is more

sensitive to changes in internal liver enzyme function than to liver perfusion.

Bupivacaine readily crosses the placenta and unbound concentration balance is quickly achieved. The degree of plasma protein binding in the foetus is lower than in the mother, which results in lower total plasma concentration in the foetus.

Bupivacaine is excreted into breast milk, but in such small quantities that there is no danger to the child.

Elimination

Bupivacaine is metabolized intensively in the liver, predominantly through aromatic hydroxylation to 4-hydroxybupivacaine and N-dealkylation to PPX, both of which are mediated by cytochrome P450 3A4. For 24 hours, about 1% of bupivacaine is eliminated in the urine as unchanged drug and 5% as PPX. During and after continuous administration of bupivacaine, the plasma concentrations of PPX and 4-hydroxybupivacaine are low in comparison with the parent drug.

Special populations

Paediatric population

In children the pharmacokinetics are similar to that in adults.

5.3 Preclinical safety data

Based on conventional studies with bupivacaine of safety pharmacology, acute and chronic toxicity, reproduction toxicity, mutagenic potential and local toxicity, no hazards for humans were identified other than those which can be expected on the basis of the pharmacodynamic action of high doses of bupivacaine (e.g. CNS signs and cardiotoxicity).

6. Pharmaceutical Particulars

6.1 List of Excipients

Glucose monohydrate
Sodium Hydroxide for pH adjustment
Hydrochloric acid for pH adjustment
Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

Unopened container: 3 years
After opening: Use immediately.

6.4 Special Precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after first opening of the medicinal product see section 6.3.

6.5 Nature and Content of container

5 ml glass (type I) ampoule. Box of 1, 5 and 10 ampoules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only. Any remaining solution should be discarded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

NEXTGEN PHARMACEUTICALS (K) LTD

8. Marketing Authorization Number

CTD10374

9. Date of first authorization/renewal of the authorization

09/07/2024

10. Date of revision of the text

14/05/2025