New Zealand Data Sheet

1 PRODUCT NAME

BUPIVACAINE SPINAL HEAVY BNM 0.5% w/v Injection, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Bupivacaine spinal heavy BNM solution for injection is a sterile, hyperbaric, isotonic aqueous solution containing bupivacaine hydrochloride monohydrate equivalent to bupivacaine hydrochloride 5 mg/mL (0.5%w/v) in water for injections.

It also contains glucose monohydrate equivalent to glucose 80 mg per mL of solution (8% w/v). It has a specific gravity of 1.03 g/mL at 20°C. The pH of the solution is adjusted with sodium hydroxide to remain between 4.0 and 6.0 during the approved shelf-life.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Bupivacaine spinal heavy BNM is a clear and colourless solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bupivacaine spinal heavy BNM is indicated for

- intrathecal (subarachnoid, spinal) anaesthesia for surgical and obstetrical procedures
- lower abdominal surgery (including caesarean section), urological and lower limb, including hip surgery, lasting 1.5 to 3 hours.

4.2 Dose and method of administration

The following dosage recommendations should be regarded as a guide for use in the average adult. The patient's physical status and concomitant medication should be considered when deciding the dose, and the lowest dose required for adequate anaesthesia should be used. Duration varies with dose, while segmental spread may be difficult to predict.

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

Dose

Spinal anaesthesia for surgery
The spread of anaesthesia obtained is dependent on several factors, the most important being volume of solution injected, position of patient and rate of injection.

• 1.5 - 4 mL Bupivacaine spinal heavy BNM (7.5-20 mg bupivacaine hydrochloride).
• When 3 mL Bupivacaine spinal heavy BNM was injected into the L3 - L4 interspace and patients were kept in the sitting position for 2 minutes before being placed supine, blockade spread to the T7 - T10 segment. When a similar injection was made in patients in the lateral position who were then immediately placed supine, blockade spread to the T4 - T7 segment.

Note:
Spinal injections should only be made after the subarachnoid space has been clearly identified by lumbar puncture. No drug should be injected until clear cerebrospinal fluid (CSF) is seen to escape from the spinal needle or it is detected by aspiration.

Hypotension
During spinal anaesthesia, a marked fall in blood pressure and/or intercostal paralysis may be seen, possibly due to the use of excessive doses or improper positioning of the patient. Hypotension and bradycardia may occur as a result of sympathetic blockade.

Standard textbooks should be consulted with respect to techniques for administration of Bupivacaine spinal heavy BNM for spinal anaesthesia.

Paediatric population
Bupivacaine spinal heavy BNM 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 block as compared to adults.

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

4.3 Contraindications

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

ABSOLUTE
1. Allergy or hypersensitivity to amide type local anaesthetics. Detection of suspected sensitivity by skin testing is of limited value.
2. Acute active diseases of the cerebrospinal system such as meningitis, tumours (primary or secondary), poliomyelitis, subacute combined degeneration of the spinal cord, cranial haemorrhage, demyelinating disease and raised intracranial pressure.

3. Spinal stenosis and active disease (e.g. spondylitis, tuberculosis, tumour) or recent trauma (e.g. facture) in the vertebral column.
4. Local anaesthetic techniques must not be used when there is inflammation and/or sepsis in the region of the proposed injection or in the presence of septicaemia.
5. Uncorrected hypotension, cardiogenic or hypovolaemic shock.
6. Coagulation disorders or ongoing anti-coagulation treatment.
7. Pernicious anaemia with subacute combined degeneration of the spinal cord.

RELATIVE
Arthritis and other diseases of the vertebral column are relative contraindications due to technical difficulties in performing a spinal injection.

4.4 Special warnings and precautions for use

1. When any local anaesthetic agent is used, resuscitative equipment and agents, including oxygen, should be immediately available in order to manage possible adverse reactions involving the cardiovascular, respiratory or central nervous systems.
2. The safety and effectiveness of Bupivacaine spinal heavy BNM depend on proper dosage, correct technique and adequate precautions. Standard textbooks should be consulted for specific techniques and precautions for spinal anaesthetic procedures. If signs of acute systemic toxicity or total spinal block appear, injection of the local anaesthetic should be stopped immediately.
3. 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.
4. The possibility of hypotension and bradycardia following epidural or subarachnoid blockade should be anticipated and appropriate precautions taken, including the prior establishment of an intravenous line and the availability of vasopressor agents and oxygen. Hypotension is common in patients with hypovolaemia due to haemorrhage or dehydration and in those with aortocaval occlusion due to abdominal tumours or the pregnant uterus in late pregnancy. Hypotension is poorly tolerated by patients with coronary or cerebrovascular disease.
5. Bupivacaine should be used with caution in patients with known medicine sensitivities.
6. Bupivacaine should be used with caution in patients with genetic predisposition to malignant hyperthermia as the safety of amide local anaesthetic agents in these patients has not been fully established. A standard protocol for the management of malignant hyperthermia should be available.
7. Spinal anaesthesia can be unpredictable and very high blocks are sometimes encountered with paralysis of the intercostal muscles, and even the diaphragm, especially in pregnancy. On rare occasions it will be necessary to assist or control ventilation.
8. Chronic neurological disorders, such as multiple sclerosis, hemiplegia due to stroke etc. are not thought to be adversely affected by spinal anaesthesia but call for caution.
9. There is an increased risk for high or total spinal blockade in the elderly and in patients in the late stages of pregnancy. The dose should therefore be reduced in these patients (see section 4.2 Dose and method of administration).

10. Intrathecal anaesthesia may lead to hypotension and bradycardia. The risk of such effects can be reduced, eg. by injecting a vasopressor. Hypotension should be treated promptly with a sympathomimetic intravenously, repeated as necessary.

4.5 Interaction with other medicines and other forms of interaction

Bupivacaine should be used with caution in patients receiving agents structurally related to local anaesthetics, e.g. certain anti-arrhythmics such as lignocaine, mexiletine, tocainide, since the systemic toxic effects are additive. Specific interaction studies with bupivacaine and anti-arrhythmic medicines class III (e.g. amiodarone) have not been performed, but caution should be advised.

4.6 Fertility, pregnancy and lactation

Pregnancy

It is reasonable to assume that a large number of pregnant women and women of child-bearing age have been given bupivacaine. No specific disturbances to the reproductive process have so far been reported, e.g. no increased incidence of malformations.

It should be noted that the dose should be reduced in patients in the late stages of pregnancy (see section 4.2 Dose and method of administration).

Local anaesthetics cross the placental barrier rapidly. A lower foetal/maternal ratio (0.2 - 0.4) than for other local anaesthetics has been observed for bupivacaine.

Breastfeeding

With recommended doses, bupivacaine enters breast milk in such small quantities that there is generally no risk of affecting the breast-fed child.

At maternal serum levels of up to 0.45 µg/mL produced by the epidural use of bupivacaine for vaginal delivery, bupivacaine could not be detected in breast milk during the first 24 hours after delivery (detection limit 0.02 µg/mL).

Fertility

No information held by the sponsor.

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 coordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

The adverse reaction profile for spinal administration of bupivacaine 0.5% is similar to those for other long acting local anaesthetics administered intrathecally. Adverse reactions caused by the drug *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. nerve trauma) or indirectly (e.g. epidural abscess) by the needle puncture or events associated to cerebrospinal leakage (e.g. postdural puncture headache).

Table of Adverse Drug Reactions

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

High or total spinal blockade
Severe adverse reactions following spinal bupivacaine are rare but may occur in connection with extensive (total) spinal blockade. Total spinal blockade will result in cardiovascular and respiratory depression. The cardiovascular depression is caused by an extensive sympathetic blockade which may result in profound hypotension and bradycardia, or even cardiac arrest. Ventilatory depression is caused by blockade of respiratory muscles including the diaphragm.

Acute systemic toxicity
In view of the low dosage employed, systemic adverse reactions are rarely associated with spinal anaesthesia. The following types are the most commonly reported:

Central nervous system
CNS manifestations are excitatory and/or depressant and may be characterised by light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred vision, nausea, vomiting, sensations of heat, cold or numbness, urinary

retention, paraesthesia, dysaesthesia, twitching, tremors, convulsions, unconsciousness, respiratory depression and/or arrest, agitation, difficulty swallowing and slurred speech.

The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest. Drowsiness following administration of bupivacaine is usually an early sign of a high blood level of the drug and may occur as a result of rapid absorption. In unconscious patients, circulatory collapse should be watched as CNS effects may not be apparent as an early manifestation of toxicity may in some cases progress to frank convulsions and ultimately lead to respiratory depression and/or arrest. It is crucial to have resuscitative equipment and anticonvulsant drugs available to manage such patients. (see section 4.9 Overdose)

Cardiovascular
Cardiovascular manifestations are usually depressant and are characterised by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

Haemodynamic
Regional anaesthesia may lead to maternal hypotension.

Allergy
Allergic reactions are characterised by cutaneous lesions, urticaria, oedema or anaphylactoid reactions. Allergy to amide type local anaesthetics is very rare. If such a reaction occurs, it should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Neurological reactions
The incidences of adverse reactions associated with the use of local anaesthetics may be related to the total dose of local anaesthetic administered and are also dependent on the particular drug used, the route of administration and the physical status of the patient.

Adverse effects experienced subsequent to spinal administration of local anaesthetic may include spinal block of varying magnitude (including total spinal block), hypotension secondary to spinal block, loss of bladder and bowel control and loss of perineal sensation and sexual function. Persistent motor, sensory and/or autonomic (sphincter control) deficit of some lower spinal segments with slow recovery (several months) or incomplete recovery have been reported in rare instances.

Pronounced acidosis, hyperkalaemia, hypocalcaemia or hypoxia in the patient may increase the risk and severity of toxic reactions.

The effects of systemic overdose and unintentional intravascular injection may involve the central nervous system and/or the cardiovascular system (see section 4.9 Overdose). Inadvertent subarachnoid injection of high doses of local anaesthetic may lead to CNS depression, respiratory arrest and cardiovascular collapse.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare

professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Acute emergencies associated with the use of local anaesthetics are generally related to high plasma levels (see section 4.8 Undesirable effects and 4.5 Interactions with other medicines and other forms of interactions). Since the dose required for spinal anaesthesia is so small (20% or less than that required for epidural anaesthesia), acute systemic toxicity is extremely unlikely and has not been reported.

With accidental intravascular injections of local anaesthetics, the toxic effects will be obvious within 1 - 3 minutes. With overdosage, peak plasma concentrations may not be reached for 20 - 30 minutes, depending on the site of injection and toxic signs will be delayed. Toxic reactions mainly involve the central nervous and cardiovascular systems.

Symptoms of acute toxicity

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis and tinnitus. Visual disturbances and muscular tremors are more serious and precede the onset of generalised convulsions. These signs must not be mistaken for neurotic behaviour.

Unconsciousness and grand mal convulsions may follow. These may last from a few seconds to several minutes. Hypoxia and hypercapnia occur rapidly following convulsions due to increased muscular activity, together with the interference with normal respiration and loss of the airway. In severe cases, apnoea may occur. Acidosis, hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

Recovery is due to redistribution of the local anaesthetic drug from the central nervous system and metabolism. Recovery may be rapid unless large amounts of the drug have been injected.

Cardiovascular toxicity indicates a more severe situation. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics.

Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anaesthetic or is heavily sedated with drugs such as benzodiazepines or barbiturates.

Treatment of overdosage

If signs of acute systemic toxicity appear, injection of the local anaesthetic should be immediately stopped.

If convulsions occur then immediate attention is required for the maintenance of patent airway and assisted or controlled ventilation with oxygen, via a positive airway pressure delivery system mask. Adequacy of the circulation should then be evaluated, bearing in

mind that drugs used to treat convulsions depress the circulation when administered intravenously.

Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, appropriate anticonvulsant medication such as an ultra-short acting barbiturate (e.g. thiopentone) or a benzodiazepine (e.g. diazepam) may be administered IV. The clinician should be familiar with these anticonvulsant drugs prior to use of local anaesthetics.

If ventricular fibrillation or cardiac arrest occurs, effective cardiovascular resuscitation treatment must be instituted and maintained for a prolonged period if necessary. Optimal oxygenation and ventilation, and circulatory support as well as treatment of acidosis are of vital importance.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Bupivacaine is a local anaesthetic of the amide type, chemically related to mepivacaine. Bupivacaine, like other local anaesthetics, causes a reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the nerve membrane. Local anaesthetics of the amide type are thought to act within the sodium channels of the nerve membrane.

Given as a spinal anaesthetic, bupivacaine has a rapid onset and a medium to long duration. The duration is dose-dependent. It is approximately four times more potent and toxic than lignocaine.

Bupivacaine spinal heavy BNM has a rapid onset and long duration of action. The duration of analgesia from the hyperbaric solution is between 2 - 3 hours in the T10 - T12 segments.

Bupivacaine spinal heavy BNM produces moderate muscle relaxation in the lower extremities lasting 2 - 3 hours. Motor blockade of the abdominal muscles makes the solution suitable for performance of abdominal surgery lasting 1.5 - 2 hours. The duration of motor blockade does not exceed the duration of analgesia.

Bupivacaine spinal heavy BNM is hyperbaric and its initial spread in the subarachnoid space is affected by gravity. The duration of anaesthesia tends to be shorter due to the larger intrathecal distribution and the consequently lower mean concentration.

5.2 Pharmacokinetic properties

Bupivacaine has a pKa of 8.1 and is extensively bound to plasma proteins (95%). Bupivacaine exhibits a high degree of lipid solubility with an oil/water partition coefficient of 27.5. These factors contribute to its prolonged duration of action.

The rate of hydrolysis in spinal fluid is slow. The majority of a dose is removed from the subarachnoid space by the venous drainage system and a smaller amount through the lymphatic system.

The maximum plasma concentration is approximately 0.4 mg/L for every 100 mg injected, this is due to slow absorption from the subarachnoid space and the small dose required for spinal anaesthesia. This means that even the maximum recommended dose (20 mg) would result in plasma levels of less than 0.1 mg/L.

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 0.40. Clearance of bupivacaine is almost entirely due to liver metabolism, and depends upon both liver blood flow and enzyme activity. The major pathway is thought to be N-dealkylation to 2,6-pipecoloxylidide (PPX). Only 6% of bupivacaine is excreted unchanged in the urine, the main metabolites being PPX and its derivatives.

Unbound bupivacaine readily crosses the placenta in equilibrium with the mother. Only about 5% of bupivacaine is unbound and available for transfer and foetal protein binding is low compared to the mother so that the total plasma concentration (free plus bound) will be lower in the foetus than in the mother.

5.3 Preclinical safety data

Based on conventional studies with bupivacaine of safety pharmacology, single and repeated dose 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

Bupivacaine spinal heavy BNM contains glucose (8% w/v), sodium hydroxide and water for injections.

6.2 Incompatibilities

Local anaesthetics react with certain metals and cause the release of their respective ions which, if injected, may cause severe local irritation. Adequate precautions should be taken to avoid prolonged contact between Bupivacaine spinal heavy BNM and metal surfaces such as metal bowls, cannulae and syringes with metal parts.

6.3 Shelf life

3 years

Incorrect autoclaving causes decomposition of glucose which may result in a decreased duration of anaesthesia of the hyperbaric solution. It is advisable not to re-autoclave ampoules of Bupivacaine spinal heavy BNM.

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

4 mL glass ampoule in a sterile pack, in packs of 10

6.6 Special precautions for disposal and other handling

The ampoules are designed for single use only, any unused portions of solutions should be discarded. The solution should be used immediately after opening the ampoule. Solutions showing discolouration should not be used.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

BNM Group
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Phone 0800 565 633

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
16 April 2020

10 DATE OF REVISION OF TEXT

21 April 2020

Summary table of changes

Section changed	Summary of new information
6.5	Addition of information about sterile packaging