Approved Professional Information for Bupivacaine HCl 0,5 % Spinal (4 ml) Fresenius

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains 5 mg bupivacaine hydrochloride (anhydrous).

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

A clear colourless and odourless solution.

The pH of the solution is between 4,0 and 6,5.

The osmolality is between 270 and 330 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Induction of spinal anaesthesia.

4.2 Posology and method of administration

Posology

Dosages of local anaesthetics used for spinal anaesthesia vary according to the volume of the subarachnoid space (i.e. the height of the patient), the segmental level of anaesthesia desired, and the duration of anaesthesia required.

BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS is given in doses of 10 to 20 mg (2 to 4 ml) for the average adult.

The smallest effective dose should be used. Smaller doses are usually needed in the elderly, in children, in debilitated patients, in cardiac disease, and in hepatic disease.
Meticulous attention to technique is essential. Special care should be taken to avoid fast bolus injection.

The spread of anaesthesia obtained with BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS is dependent upon several factors, the most important being volume of solution injected, and the age and position of the patient.

The difference in spread between a 10 mg and 20 mg dose is approximately two segments.

The larger dose gives a half to 1 hour longer duration of anaesthesia in the lumbar segments and longer lasting motor blockade.

When injected into the sub-arachnoid space via the L_3/L_4 interspace with the patient in a sitting position, 3 ml of BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS spreads to between the T_4 and T_5 segments.

If the patient is in the supine horizontal position the blockade spreads to between the T_5 and T_7 segments.

Before administration of BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS**,** make sure that resuscitative equipment, such as equipment to maintain a free airway, oxygenation and circulation, is immediately available.

The effects of spinal administration of a dose of BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS exceeding 20 mg (4 ml) have not yet been studied and such volume can therefore not be recommended.

Method of administration

Intrathecal injection.

4.3 Contraindications

- Hypersensitivity to bupivacaine hydrochloride or to any of the excipients listed in section 6.1.
- Known hypersensitivity to any local anaesthetics of the amide-type.
- BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS is not recommended for use in intravenous regional anaesthesia, or paracervical block in obstetrics.
- 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

Intrathecal anaesthesia should only be undertaken by doctors with the necessary knowledge and experience.

Regional anaesthetic procedures should always be performed in a properly equipped and staffed area. Resuscitation equipment and medication must be available when BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS is used, 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 doctor 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 section 4.8).

Like all local anaesthetic medicines, BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS 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 medicine. This is especially the case after unintentional intravascular administration or injection into highly vascular areas.

The inadvertent intravenous injection or filtration of BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS may cause cardiac arrest and convulsions.

Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported in connection with high systemic concentrations of BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS. 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.

Cardiac arrest due to BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS can be resistant to electrical defibrillation and a successful outcome may require prolonged resuscitative efforts.

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.

BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS should be given cautiously to the elderly, the debilitated, and to patients with epilepsy, impaired cardiac conduction, shock or with liver damage; patients with myasthenia gravis are particularly susceptible to the effects of local anaesthetics.

The central nervous system and cardiac toxicity of BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS can be enhanced by hypoxia and acidosis. The use of local anaesthetics during pregnancy in the presence of fetal hypoxia or acidosis may be dangerous (see section 4.6).

Intrathecal anaesthesia can cause hypotension and bradycardia. The risk of such effects can be reduced, e.g. by injecting a vasopressor. If hypotension develops it should be treated promptly with a sympathomimetic intravenously, repeated as necessary. 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 less frequent consequence of intrathecal anaesthesia and may result in paraesthesia, anaesthesia, motor weakness and paralysis. Occasionally these are permanent.

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.

Spinal anaesthetics should be used with caution in patients with impaired cardiovascular function such as severe disturbances of cardiac rhythm, shock, heart block or congestive heart failure. Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness is advised. Convulsions and cardiovascular collapse, that may be dose-related, may result from diminished tolerance and/or rapid absorption from the injection site.

Cranial nerve lesions have also occurred after spinal anaesthesia. Reversible loss of hearing in the low frequency range, usually affecting both ears, has been reported following spinal anaesthesia.

Patients treated with antidysrhythmic medicines 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).

BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS contains sodium

BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS contains 3,15 mg sodium per ml, equivalent to 0,16 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric population

BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS should be given cautiously to children.

4.5 Interaction with other medicines and other forms of interaction

Pre-treatment with Histamin H_2-receptor antagonists like cimetidine, can decrease the clearance of BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS or has no significant pharmacokinetic effects. Similarly, pre-treatment with ranitidine can either increase plasma concentrations of bupivacaine or has no significant effect.

BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS should be used with caution in patients receiving other local anaesthetics such as lidocaine (lignocaine), or medicines structurally related to amide-type local anaesthetics e.g. certain antidysrhythmics such as mexiletine, since systemic toxic effects are additive.

Specific interaction studies with BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS and antidysrhythmic medicines class III (e.g. amiodarone) have not been performed, but caution is advised (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Fetal intoxication can occur following the use of BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS in labour, either as a result of the transplacental diffusion or after accidental injection of the fetus.

Using BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS to produce paracervical block during labour, especially continuous block, is not recommended as serious fetal bradycardia may be produced.

The use of local anaesthetics during pregnancy in the presence of fetal hypoxia or acidosis may be dangerous.

Breastfeeding

BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS is distributed into breast milk.

4.7 Effects on ability to drive and use machines

BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS 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

a) Summary of the safety profile

Hypersensitivity reactions to BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS occur less frequently. The systemic toxicity mainly involves the central nervous system and the cardiovascular system. Excitation of the central nervous system may be manifested by restlessness, excitement, nervousness, light-headedness, dizziness, blurred vision, nausea

and vomiting, vertigo, muscle twitching and tremors, and convulsions. Numbness of the tongue and perioral region may appear as an early sign of systemic toxicity.

Excitation might be transient and followed by depression, drowsiness, respiratory failure and coma. There may be simultaneous effects on the cardiovascular system with myocardial depression and peripheral vasodilatation resulting in hypotension and bradycardia; arrhythmia and cardiac arrest may occur. Hypotension often accompanies spinal anaesthesia.

The adverse reaction profile for BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS is similar to those for other long acting local anaesthetics used for intrathecal anaesthesia.

Adverse reactions caused by the medicine *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 abscess) by needle puncture or events associated to cerebrospinal leakage (e.g. post-dural puncture headache).

b) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Infections and infestations			Septic meningitis
Immune system		Hypersensitivity	

disorders		reactions Anaphylactic shock	
Nervous system disorders	Post-dural puncture headache	Paraesthesia Paresis Dysaesthesia High or total unintentional spinal block Paraplegia Paralysis Neuropathy Arachnoiditis	Convulsions Restlessness Excitement Nervousness Light-headedness Dizziness CNS depression Drowsiness Coma Headache Cranial nerve lesions Persistent anaesthesia Meningismus Cranial nerve palsies Trauma or compression of the spinal cord Haematoma of the spinal cord Abscess of the spinal cord Cauda equina

			syndrome
Eye disorders			Blurred vision Photophobia
Ear and labyrinth disorders			Vertigo Tinnitus Reversible hearing loss
Cardiac disorders	Hypotension Bradycardia	Cardiovascular arrest	Cardiovascular collapse Myocardial depression Decreased cardiac output Arrhythmia
Vascular disorders			Peripheral vasodilatation Venodilatation Reduced venous return
Respiratory, thoracic and mediastinal disorders		Respiratory depression	Respiratory failure
Gastrointestinal disorders	Nausea	Vomiting	Numbness of the tongue Numbness of the perioral region

			Loss of sphincter control Faecal incontinence
Musculoskeletal and connective tissue disorders		Muscle weakness Back pain	Muscle twitching Tremors
Renal and urinary disorders	Urinary retention Urinary incontinence		
Pregnancy, puerperium and perinatal conditions			Fetal intoxication Fetal bradycardia Slowing of labour Increased incidence of forceps delivery
Reproductive system and breast disorders			Loss of perineal sensation Loss of sexual function
General disorders and administrative site conditions			Shivering

c) Description of selected adverse reactions

Acute systemic toxicity

Bupivacaine HCl 0,5 % Spinal (4 ml) Fresenius, 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

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 mg to 150 mg intravenously or with diazepam 5 mg to 10 mg intravenously. Alternatively, succinylcholine 50 mg to 100 mg intravenously may be given but only if the doctor 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 mg to 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.

d) 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

Health care providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

Reporting suspected adverse reactions after authorisation of BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS is important. It allows continued monitoring of the benefit/risk balance of BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS. Health care providers are asked to report any suspected adverse reactions via the **Adverse Drug Reaction Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Numbness of the tongue and perioral region is an early sign of toxicity. Serious fetal bradycardia may occur. Overdosage should be treated symptomatically and supportive. When systemic reactions to local anaesthetics occur steps should be taken to maintain the circulation and respiration and to control convulsions. A patent airway must be established, and oxygen given, together with assisted ventilation if necessary. The circulation should be maintained with infusions of intravenous fluids.

Cardiac arrest due to BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS can be resistant to electrical defibrillation and a successful outcome may require prolonged

resuscitative efforts. Resuscitation equipment and medication should always be at hand for emergencies.

See also section 4.8 "**Acute systemic toxicity**" and "**Treatment of acute systemic toxicity**".

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A4 - Local anaesthetics.

Pharmacotherapeutic group: Anaesthetics, local; amides.

ATC code: N01BB01.

Mechanism of action:

Bupivacaine is a long acting (up to 8 hours) local anaesthetic of amide-type with an intermediate, to slow onset (about 15 minutes) of action. Bupivacaine blocks conduction by decreasing or preventing the large transient increase in the permeability of the membrane to sodium ions, by means of a slight depolarisation of the membrane. The permeability of a resting nerve to both potassium and sodium ions is reduced.

5.2 Pharmacokinetic properties

Bupivacaine penetrates the tissues as an unprotonated amine. Bupivacaine is not detoxified by plasma esterases; detoxification takes place in the liver via conjugation with glucuronic acid. Bupivacaine is about 95 % bound to plasma proteins. The half-life ranges from 1,5 to 5,5 hours in adults and about 8 hours in neonates. It is metabolised in the liver and is excreted in the urine principally as metabolites with only 5 to 6 % as unchanged medicine.

Bupivacaine is excreted into breast milk in small quantities and crosses the placenta but the ratio of fetal concentrations to maternal concentrations is relatively low. Bupivacaine also diffuses into the cerebrospinal fluid.

Paediatric population

In children the pharmacokinetics are similar to that in adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injection

6.2 Incompatibilities

BUPIVACAINE HCl 0,5 % SPINAL (4 ml) FRESENIUS should not be mixed with other medicines.

6.3 Shelf life

24 months.

In-use shelf life: Use immediately after opening.

6.4 Special precautions for storage

Store at or below 25 °C.

Any unused portion should be discarded.

For storage of the opened product, see section 6.3.

6.5 Nature and contents of container

4 ml solution in 5 ml clear glass ampoules. Pack size of 10 ampoules in an outer cardboard carton.

6.6 Special precautions for disposal and other handling

Any unused portion should be discarded. If the solution contains a precipitate or is discoloured it should not be used.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi Manufacturing SA (Pty) Ltd

6 Gibaud Road

Korsten 6020

Gqeberha

South Africa

8. REGISTRATION NUMBER

29/4/0558

9. DATE OF FIRST AUTHORISATION

11 November 1995

10. DATE OF REVISION OF THE TEXT

25 May 2023.