**APPROVED PROFESSIONAL INFORMATION**

**SCHEDULING STATUS**

**S4**

## 1 NAME OF THE MEDICINE

**BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS** solution for injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml contains 50 mg bupivacaine hydrochloride.

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

BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS is used as a peripheral nerve block, caudal or epidural block.

### 4.2 Posology and method of administration

**Posology**

The area and vascularity of the tissue, the amount of neuronal segments to be blocked, the

technique of anaesthesia as well as personal tolerance to BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS are factors that need to be taken into account when administering BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS.

When the correct dose of BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS is administered, complete sensory blockage will occur; however, motor blockade depends on the dose of BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS administered. The duration of anaesthesia is such that in most cases, a single dose will be sufficient.

The following dosages are recommended as a guide for use and have generally proved satisfactory in the average adult:

<table>
<tr><th>Procedure</th><th colspan="2">Dose</th><th>Additional Info</th></tr>
<tr><td></td><td>ml</td><td>mg</td><td></td></tr>
<tr><td>Trigeminal block</td><td>0,5 – 4</td><td>2,5 - 20</td><td></td></tr>
<tr><td>Axillary block</td><td>15 – 30</td><td>75 – 150</td><td></td></tr>
<tr><td>Intercostal block</td><td>3 – 5</td><td>15 – 25</td><td>Dose indicated for every segment</td></tr>
<tr><td>Epidural anaesthesia</td><td>10 - 20</td><td>50 – 100</td><td></td></tr>
<tr><td colspan="2">Continuous epidural anaesthesia</td><td colspan="2">Starting dose of 10 ml followed by 3 ml – 5 ml – 8 ml every 4 – 6 hours. The dose depends on the number of segments to be rendered analgesic and the patient’s age.</td></tr>
<tr><td>Caudal anaesthesia</td><td>15 - 30</td><td>75 - 150</td><td></td></tr>
</table>

The maximum recommended dose of BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS in a single

injection is 150 mg and should not be exceeded unless there are special considerations present. Where dosage is calculated on the patient's mass, this should not exceed 2 mg/kg body mass up to a maximum of 150 mg.

**Special populations**

Patients treated with antidysrhythmic medicines class III (e.g., amiodarone) should be under close surveillance and ECG monitoring, since cardiac effects may be additive (see section 4.5).

**Elderly population**

Doses should be reduced in elderly or debilitated patients (refer to section 4.4).

**Paediatric population**

BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS is not recommended for children younger than 12 years.

**Method of administration**

Injection.

The utmost care should be taken to prevent an accidental intravascular injection, always including careful aspiration.

## 4.3 Contraindications

- Hypersensitivity to bupivacaine or to any of the excipients (see section 6.1).
- Known hypersensitivity to local anaesthetic medicines of the amide type.
- Intravenous regional anaesthesia (Bier's block).
- Epidural anaesthesia, regardless of the local anaesthetic used, has its own general 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.

- Tuberculosis of the spine.
- 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**

**DURING LOCAL ANAESTHESIA RESUSCITATIVE MEDICINES AND EQUIPMENT MUST BE PRESENT AT ALL TIMES.**

Before any nerve block is attempted, intravenous access for resuscitation purposes should be established. Medical practitioners should have received adequate and appropriate training in the procedure to be performed and should be familiar with the diagnosis and treatment of side effects, systemic toxicity or other complications (see section 4.9).

Paracervical block with amide-type local anaesthetics, such as BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS, during labour often precedes foetal bradycardia and may be associated with foetal acidosis. The risk increases with premature birth, toxaemia of pregnancy, and foetal l distress. Paracervical block using BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS is not recommended.

There have been reports of cardiac arrest during the use of bupivacaine, as in BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS, for epidural anaesthesia or peripheral nerve blockade where resuscitative efforts have been difficult and were required to be prolonged before the patient responded.

BUPIVACAINE HCl 0,5 % (10 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 bupivacaine. This is especially the case after unintentional intravascular administration. Ventricular dysrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported in connection with high systemic concentrations of bupivacaine.

Major peripheral nerve blocks may require the administration of a large volume of local anaesthetic in areas of high vascularity, often close to large vessels where there is an increased risk of intravascular injection and/or systemic absorption. This may lead to high plasma concentrations.

Overdosage or accidental intravenous injection may give rise to toxic reactions.

Injection of repeated doses of BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS may cause significant increases in blood levels with each repeated dose due to accumulation of bupivacaine. Tolerance varies with the status of the patient.

**Patients at risk and risks associated with certain anaesthesia techniques:**

- Debilitated, elderly or acutely ill patients should be given reduced doses to commensurate with their physical status.
- Patients with partial or complete heart block – due to the fact that local anaesthetics may depress myocardial conduction.
- Patients with advanced liver disease or severe renal dysfunction.
- Patients in the late stages of pregnancy.
- Caution is advised for co-administration of BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS and anti-dysrhythmic medicines class III, e.g. amiodarone (see section 4.5).
- Patients allergic to ester-type local anaesthetic medicines (procaine, tetracaine, benzocaine, etc.) have not shown cross-sensitivity to medicines of the amide-type such as bupivacaine.

- Local anaesthetics such as BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS should be used with caution for epidural anaesthesia inpatients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by these medicines.
- The physiological effects generated by a central neural blockade are more pronounced in the presence of hypotension. Patients with hypovolaemia due to any cause can develop sudden and severe hypotension during epidural anaesthesia. Epidural anaesthesia should therefore be avoided or used with caution in patients with untreated hypovolaemia or significantly impaired venous return.
- Retrobulbar injections may reach the cranial subarachnoid space causing serious/severe reactions, including temporary blindness, cardiovascular collapse, apnoea and convulsions.
- Retro- and peribulbar injections of local anaesthetics carry a low risk of persistent ocular muscle dysfunction. The primary causes include trauma and/or local toxic effects on muscles and/or nerves. The severity of such tissue reactions is related to the degree of trauma, the concentration of the local anaesthetic and the duration of exposure of the tissue to the local anaesthetic. For this reason, as with all local anaesthetics, the lowest effective concentration and dose of local anaesthetic should be used.
- Vasoconstrictors may aggravate tissue reactions and should be used only when indicated.
- Small doses of local anaesthetics injected into the head and neck, including retrobulbar, dental and stellate ganglion blocks, may produce systemic toxicity due to inadvertent intra-arterial injection.
- There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics. The majority of reported cases of chondrolysis have involved the shoulder joint. Due to multiple contributing factors and inconsistency in the scientific literature regarding mechanism of action, causality has not been established. Intra-articular continuous infusion is not an approved indication for BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS.

Epidural anaesthesia can cause intercostal paralysis and patients with pleural effusions may suffer respiratory distress.

Epidural anaesthesia with BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS can cause hypotension and bradycardia which should be anticipated and appropriate precautions taken. These may include pre-loading the circulation with crystalloid or colloid solution. If hypotension develops it should be treated with a suitable vasopressor 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 epidural anaesthesia.

The physiological effects generated by a central neural blockade are more pronounced in the presence of hypotension. Patients with hypovolaemia due to any cause can develop sudden and severe hypotension during epidural anaesthesia. Epidural anaesthesia should therefore be avoided or used with caution in patients with untreated hypovolaemia or significantly impaired venous return.

When administering repeat doses of BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS, precaution should be taken with patients with severe liver disease (see section 5.2). If signs of hepatic dysfunction are observed during the treatment with BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS, the medicine should be discontinued.

Septicaemia can increase the risk of intraspinal abscess formation in the post-operative period

(see section 4.3).

**BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS contains sodium:**

BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS contains 8,15 mg sodium per ml, equivalent to 0,4 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

**Paediatric population**

BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS is not recommended for children under 12 years of age.

**4.5 Interaction with other medicines and other forms of interaction**

BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS should be used with caution in patients receiving other local anaesthetics or medicines structurally related to amide-type local anaesthetics, e.g. certain antidysrhythmics, such as lidocaine (lignocaine), since systemic toxic effects are additive (see section 4.2).

Specific interaction studies with bupivacaine and antidysrhythmic medicines class III (e.g., amiodarone) have not been performed, but caution should be advised (see also section 4.4).

Propranolol may reduce the clearance of BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS. There is a risk of increased bupivacaine toxicity when these medicines are used concomitantly.

There is a possible risk that the adverse effects of BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS on the heart may be enhanced in patients taking calcium-channel blockers.

Interactions between BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS and histamine $H_2$-antagonists, such as cimetidine and ranitidine, resulted in a decreased clearance of bupivacaine and an increased plasma concentration, respectively, but had no significant clinical effects.

## 4.6 Fertility, pregnancy, and lactation

**Pregnancy**

Safe use in pregnancy and lactation, other than for use in labour, has not yet been established (see section 4.5).

**Breastfeeding**

Bupivacaine, the active ingredient of BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS, is distributed into breast milk.

## 4.7 Effects on ability to drive and use machines

Besides the direct anaesthetic effect on sensory and motive functioning, BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS may have an 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**

Severe systemic side effects may occur when BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS is accidentally injected intravascularly.

**b) Tabulated summary of adverse reactions** ‘

| **MedDRA system organ class** | **Frequency** | **Adverse reactions** |
|---|---|---|
| Immune system disorders | Less frequent | Allergic reactions, anaphylactic reaction/shock. |
| Psychiatric disorders | Less frequent | Excitation, depression, nervousness. |
| Nervous system disorders | Frequent | Paraesthesia, dizziness. |
| | Less frequent | Convulsions, circumoral paraesthesia, numbness of the tongue, hyperacusis, visual disturbances, loss of consciousness, tremors, light-headedness, dysarthria, muscle twitching, chills, fever, drowsiness, neurological damage, neuropathy, peripheral nerve injury, arachnoiditis, paresis and paraplegia. |
| Eye disorders | Less frequent | Constriction of the pupils, diplopia, blurred vision. |
| Ear and labyrinth disorders | Less frequent | Tinnitus. |
| Cardiac disorders | Frequent | Bradycardia. |
| | Less frequent | Myocardial depression, arrhythmia, cardiac arrest, oedema, ventricular dysrhythmias. |

| **MedDRA system organ class** | **Frequency** | **Adverse reactions** |
|---|---|---|
| Vascular disorders | Frequent | Changes in blood pressure (usually hypotension), hypertension. |
| Respiratory, thoracic and mediastinal disorders | Less frequent | Respiratory depression. |
| Gastrointestinal disorders | Frequent | Nausea, vomiting. |
| Hepato-biliary disorders | Less frequent | Hepatic dysfunction, with reversible increase of liver enzymes and bilirubin. |
| Skin and subcutaneous tissue disorders | Less frequent | Pruritus, urticaria, skin rash. |
| Renal and urinary disorders | Frequent | Urinary retention. |
| General disorders and administration site conditions | Less frequent | Skin or intravenous reaction may occur at the site of injection if the patient shows sensitivity to BUPIVACAINE HCl 0,5 % (10 ml) FRESENIUS.<br>Accidental sub-arachnoid injection can lead to very high spinal anaesthesia possibly with apnoea and severe hypotension. |

**c. Description of selected adverse reactions**

***Acute systemic toxicity***

Systemic toxic reactions primarily involve the central nervous system (CNS) and the cardiovascular system. Such reactions are caused by high blood concentrations of a local anaesthetic, which may appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularised areas (see section 4.4). CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the medicinal product, both quantitatively and qualitatively.

***Central nervous system toxicity*** is a graded response with symptoms and signs of escalating severity. The first symptoms are usually circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis, tinnitus and visual disturbances. Dysarthria, muscular twitching or 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, which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with respiration and possible loss of functional airways. 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 medicinal product from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the medicine have been injected.

***Cardiovascular system toxicity*** may be seen in severe cases and is generally preceded by signs of toxicity in the central nervous system. In patients under heavy sedation or receiving a general anaesthetic, prodromal CNS symptoms may be absent. Hypotension, bradycardia,

dysrhythmia, and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics, but in rare cases cardiac arrest has occurred without prodromal CNS effects.

***Treatment of acute toxicity:***

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

Treatment of a patient with systemic toxicity consists of arresting convulsions and ensuring adequate ventilation with oxygen, if necessary, by assisted or controlled ventilation (respiration). Once convulsions have been controlled and adequate ventilation of the lungs ensured, no other treatment is generally required.

If cardiovascular depression occurs (hypotension, bradycardia) appropriate treatment with intravenous fluids, vasopressor, inotropic medicines and/or lipid emulsion should be considered.

If circulatory arrest should occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

Cardiac arrest due to bupivacaine can be resistant to electrical defibrillation and resuscitation must be continued energetically for a prolonged period.

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

*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 % (10 ml)

FRESENIUS is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

### 4.9 Overdose

Accidental intravascular injections of local anaesthetics may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, systemic toxicity appears later (15 –60 minutes after injection) due to the slower increase in local anaesthetic blood concentration.

***Treatment of overdose:***

Maintenance of the airways and ventilation with oxygen of the patient during respiratory distress.

Treatment of milder symptoms of systemic toxicity may not be required but if convulsions occur, they can be controlled with oxygen and by rapid intravenous administration of a suitable benzodiazepine or a short-acting barbiturate e.g. thiopentone 100 mg – 200 mg or diazepam 5 mg –10 mg.

During circulatory distress intravenous fluids, and when necessary, vasopressors can be administered.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Category and class: A 4 Local anaesthetics.

Pharmacotherapeutic group: Anaesthetics, local; amides.

ATC code: N01BB01.

Bupivacaine is an amide-type local anaesthetic medicine. Bupivacaine effects local anaesthetic action by preventing the initiation and transmission of neural impulses by stabilising the neuronal membrane.

The onset of action after administration is 10 – 40 minutes and the effect may last for several hours. Bupivacaine has a tendency to provide more sensory blockage than motor blockade.

### 5.2 Pharmacokinetic properties

Reported serum half-lives are from 1,5 to 5,5 hours in adults. Bupivacaine is about 95 % bound to plasma proteins. It is metabolised in the liver and is excreted in the urine mainly as metabolites, with only 5 – 6 % as unchanged bupivacaine.

### 5.3 Preclinical safety data

Not applicable.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride

Water for Injections.

### 6.2 Incompatibilities

BUPIVACAINE HCl 0,5 % (10 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

Clear colourless solution in clear 10 ml glass ampoules.

Packs 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

W/4/335

## 9 DATE OF FIRST AUTHORISATION

23 April 1990

## 10 DATE OF REVISION OF THE TEXT

17 September 2022