PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml contains: Bupivacaine hydrochloride monohydrate equivalent to bupivacaine hydrochloride anhydrous 50 mg.

For a full list of excipients, see section 6.1.

Sugar free.

3 PHARMACEUTICAL FORM

Solution for injection.

A clear, colourless, or almost colourless solution in 10 ml clear colourless glass ampoules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml 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 number of neuronal segments to be blocked, the technique of anaesthesia as well as personal tolerance to PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml are factors that need to be considered when administering PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml.

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

When the correct dose of PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml is administered, complete sensory blockage will occur; however, motor blockade depends on the dose of PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml 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.

Procedure:	**Dose:**		**Additional Info**
	ml	**mg**	
Trigeminal block	0,5 - 4	2,5 - 20	
Axillary block	15 - 30	75 - 150	
Intercostal block	3 - 5	15 - 25	The dose indicated is for every segment.
Epidural anaesthesia	10 - 20	50 - 100	
Continuous epidural anaesthesia		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.	
Caudal anaesthesia	15 – 30	75 – 150	

The maximum recommended dose of PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml 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 anti-dysrhythmic medicines class III (e.g., amiodarone) should be under close surveillance and ECG monitoring, since cardiac effects may be additive (see section 4.5).

Paediatric population

PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml is not recommended for children younger than 12 years.

4.3 Contraindications

- Hypersensitivity to bupivacaine hydrochloride 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).

There have been reports of cardiac arrest during the use of bupivacaine, as in PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml, for epidural anaesthesia or peripheral nerve blockade where resuscitative efforts have been difficult and were required to be prolonged before the patient responded.

Bupivacaine, as in PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml, 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.

PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml appears to be more cardiotoxic than other local anaesthetics. Fatalities have occurred since toxicity is difficult to treat. The central nervous system and cardiac toxicity can be enhanced by hypoxia and acidosis.

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

Paracervical block with amide-type local anaesthetics, such as PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml, 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 PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml is not recommended.

Inappropriate positioning of the patient may be a contributory factor for women in labour.

Injection of repeated doses of PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml 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, as well to patients with epilepsy or acutely ill patients should be given reduced doses to commensurate with their physical status.
- Patients with impaired cardiac conduction, partial or complete heart block – due to the fact that local anaesthetics may depress myocardial conduction.
- Patients with impaired and/or hepatic damage or advanced liver disease or severe renal dysfunction.
- Patients in the late stages of pregnancy.
- Caution is advised for co-administration of PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml 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 PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml should be used with caution for epidural anaesthesia in patients 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 PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml.
- Patients with myasthenia gravis may be particularly susceptible to the effects of local anaesthetics.

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

Epidural anaesthesia with PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml 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 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 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.

Since bupivacaine is metabolised in the liver, it should be used cautiously in patients with liver disease or with reduced liver blood flow. When administering repeat doses of PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml, 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 PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml, the medicine should be discontinued.

Septicaemia can increase the risk of intraspinal abscess formation in the post-operative period (see section 4.3).

Particular caution is to be taken in case of injecting local anaesthetics into inflamed or infected areas.

4.5 Interaction with other medicines and other forms of interaction

PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml should be used with caution in patients receiving other local anaesthetics or medicines structurally related to amide-type local anaesthetics, e.g., certain anti-dysrhythmics, such as lidocaine (lignocaine), since systemic toxic effects are additive (see section 4.2).

Specific interaction studies with bupivacaine and anti-dysrhythmic 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 PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml. There is a risk of increased bupivacaine toxicity when these medicines are used concomitantly.

There is a possible risk that the adverse effects of PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml on the heart may be enhanced in patients taking calcium-channel blockers.

Interactions between PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml 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

Safe use in pregnancy and lactation, other than for use in labour, has not yet been established (see section 4.4).

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

Foetal bradycardia frequently follows paracervical block with some amide-type local anaesthetics and may be associated with foetal acidosis.

Added risk appears to be present in prematurity, toxaemia of pregnancy and foetal distress.

Breastfeeding

Bupivacaine is distributed into breast milk, but in such small quantities that there is no risk of affecting the child at therapeutic dose levels.

4.7 Effects on ability to drive and use machines

Besides the direct anaesthetic effect on sensory and motive functioning, PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml 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.

Patients should be instructed that they should avoid potentially hazardous tasks such as driving and operating machinery until they know how PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml affects them.

4.8 Undesirable effects

a. Summary of the safety profile

PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml may have side effects:

- side effects apparent after local anaesthesia may be due to the anaesthetic or to errors in technique or may be the result of blockade of the sympathetic nervous system.
- local anaesthetics may have systemic adverse effects as a result of the raised plasma concentrations, which ensue when the rate of absorption into the circulation exceeds the rate of breakdown.

b. Tabulated summary of adverse reactions

The frequency of adverse reactions listed below is defined using the following convention: frequent; less frequent or frequency unknown (cannot be estimated from the available data).

MedDRA system organ class	**Frequency**	**Adverse reactions**
Immune system disorders	Less frequent	Allergic reactions (characterized by cutaneous lesions (e.g., urticaria), oedema and other manifestations of allergy), 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 and perioral region, hyperacusis, blurred vision, 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, 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.

c. Description of selected adverse reactions

Skin or intravenous reaction may occur at the site of injection if the patient shows sensitivity to PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml.

Accidental sub-arachnoid injection can lead to very high spinal anaesthesia possibly with apnoea and severe hypotension.

Acute systemic toxicity

Systemic toxic reactions of local anaesthetics mainly 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 medicine, 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 medicine 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 CNS. 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 agents 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

Reporting suspected adverse reactions after authorisation of PHARMA-Q BUPIVACAINE INJECTION is important. It allows continued monitoring of the benefit/risk balance of PHARMA-Q BUPIVACAINE INJECTION. 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

Pharmacological classification: A4 Local anaesthetics.

Pharmacotherapeutic group: Anaesthetics, local; amides.

ATC code: N01BB01.

Bupivacaine hydrochloride is a local anaesthetic of the amide type. It is a potent medicine capable of producing prolonged anaesthesia due to its amide structure. Bupivacaine hydrochloride stabilizes the neuronal membrane and prevents initiation and transmission of nerve impulses, thereby acting as a local anaesthetic. When administered in recommended doses and concentrations, it does not ordinarily produce irritation or tissue damage and does not cause methaemoglobinaemia.

5.2 Pharmacokinetic properties

Absorption

The onset of action of bupivacaine hydrochloride is rapid and anaesthesia may last for several hours. The duration of action (up to 8 hours) is significantly longer than any other commonly used local anaesthetic.

Distribution

Bupivacaine hydrochloride is about 95 % bound to plasma protein. It has a half- life of 1,5 to 5,5 hours in adults and 8 hours in neonates.

Biotransformation

Due to the amide structure, bupivacaine hydrochloride is not detoxified by plasma esterases. It is metabolised in the liver.

Elimination

Bupivacaine hydrochloride 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 foetal concentration to maternal concentrations is relatively low. Bupivacaine also diffuses into the cerebrospinal fluid.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide

Water for injections.

6.2 Incompatibilities

Bupivacaine may precipitate if diluted with alkaline solutions and should not be diluted or co-administered with sodium bicarbonate injections.

PHARMA-Q BUPIVACAINE INJECTION 50 mg/10 ml should not be mixed with other medicines.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

6.5 Nature and contents of container

A clear colourless glass ampoule containing a 0,5 % *m/v* solution of bupivacaine hydrochloride in 10 ml ampoules. Pack size: 10 Ampoules per box.

6.6 Special precautions for disposal and other handling

For single use only.

The solution should be inspected visually before use.

Do not use if the solution is brown or contains a precipitate.

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMA-Q HOLDINGS (Pty) Ltd

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Industria West 2003

Johannesburg

South Africa

8 REGISTRATION NUMBER

31/4/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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