1.3.1.1.3 PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS **S4**

1 NAME OF THE MEDICINE

BUPIVACAINE HCl 0,5 % INJECTION WITH ADRENALINE 1:200 000 (as bitartrate) ADCO injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL contains:

Bupivacaine hydrochloride 5 mg and adrenaline bitartrate 0,0091 mg (5 µg/mL adrenaline).

Antioxidant: sodium metabisulphite

Sugar free

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Injection

Clear, colourless, solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BUPIVACAINE HCl 0,5 % INJECTION WITH ADRENALINE 1:200 000 (as bitartrate) ADCO is indicated for peripheral nerve block, caudal or epidural block.

4.2 Posology and method of administration

Posology

Dosage varies and depends upon the area to be anaesthetised, the vascularity of the tissues, the number of neuronal segments to be blocked, individual tolerance and technique of anaesthesia.

In recommended doses, BUPIVACAINE HCl 0,5 % INJECTION WITH ADRENALINE 1:200 000 (as bitartrate) ADCO produces complete sensory block, but the effect on motor function differs depending on volume utilised. The duration of anaesthesia is such that for most indications, a single dose is sufficient.

The dosages of BUPIVACAINE HCl 0,5 % INJECTION WITH ADRENALINE 1:200 000 (as bitartrate) ADCO in the table below have generally proved satisfactory and are recommended as a guide for use in the average adult.

Procedure	Dose		Remarks
	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	Initially 10 mL followed by 3 – 5 – 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 BUPIVACAINE HCl 0,5 % INJECTION WITH ADRENALINE 1:200 000 (as bitartrate) ADCO 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.

Paediatric population

Until further experience is gained, BUPIVACAINE HCl 0,5 % INJECTION WITH ADRENALINE 1:200 000 (as bitartrate) ADCO is not recommended for children younger than 12 years.

Method of administration

Injection

4.3 Contraindications

- BUPIVACAINE HCl 0,5 % INJECTION WITH ADRENALINE 1:200 000 (as bitartrate) ADCO is contraindicated in patients with known sensitivity to bupivacaine and adrenaline or to any of the excipients listed in section 6.1
- Bupivacaine is contraindicated for use in intravenous regional anaesthesia (Bier's block) and for paracervical block in obstetrics
- Solutions containing adrenaline are contraindicated in patients with hyperthyroidism or severe heart disease particularly when tachycardia is present
- Solutions of bupivacaine containing adrenaline should not be used in connection with anaesthesia in areas of the body supplied by end arteries or otherwise having a compromised blood supply such as digits, nose, external ear or genitalia owing to the risk of tissue necrosis. Injection of bupivacaine containing adrenaline in areas of end arteries (e.g. penile block, Oberst block) may cause ischaemic tissue necrosis.
- Epidural 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, subacute 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
- Patients with an expanding cerebral lesion, a tumour, cyst or abscess, which may, if the intracranial pressure is suddenly altered, cause obstruction to the cerebrospinal fluid or blood circulation (the pressure cone).

4.4 Special warnings and precautions for use

Regional or local anaesthetic procedures should always be performed in a properly equipped and staffed area.

Equipment and medicines necessary for monitoring and emergency resuscitation should be immediately available whenever local or general anaesthesia is administered.

Patients receiving major blocks should be in an optimal condition and have an IV line inserted before the blocking procedure. The healthcare professional responsible should take the necessary precautions to avoid overdose or intravascular injection, always including careful aspiration, and be appropriately trained and familiar with the diagnosis and treatment of side effects, systemic toxicity and other complications such as marked restlessness, twitching or convulsions followed by coma with apnoea and cardiovascular collapse.

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. 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 intraarterial injection. Healthcare professionals who perform retrobulbar blocks should be aware that there have been reports of respiratory arrest following local anaesthetic injection. Prior to retrobulbar block, necessary equipment, medicines and personnel should be immediately available as with all other regional procedures.

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 medicine.
Accidental intravascular injection of bupivacaine may lead to systemic toxicity which could result in:

- Cerebral haemorrhage due to the sudden rise in blood pressure
- Convulsions leading to cardiac arrest
- Ventricular dysrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death.

Patients treated with antidysrhythmic medicines such as amiodarone should be under close surveillance and ECG monitoring, since cardiac effects may be additive.

Although regional anaesthesia is frequently the optimal anaesthetic technique, some patients require special attention in order to reduce the risk of dangerous side effects:

- The very young, elderly, acutely ill, or debilitated patients, who may be more susceptible to systemic toxicity induced by local anaesthetics
- 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 late stages of pregnancy.

Injection of repeated doses of bupivacaine hydrochloride may cause significant increases in blood levels with each repeated dose due to slow accumulation of the medicine.

Since bupivacaine is metabolised in the liver, it should be used cautiously in patients with liver disease or with reduced liver blood flow.

Local anaesthetics should be used with caution for epidural anaesthesia in the following situations:
Severe shock, dehydration, gross hypertension, marked obesity, senility, cerebral atheroma, myocardial degeneration, toxaemia, congestive heart failure, hepatic disease or impairment, cardiovascular function impairment, hypotension, hypovolaemia, history of sensitivity to bupivacaine or chemically related anaesthetics, inflammation or infection in region of injection and renal disease.

BUPIVACAINE HCl 0,5 % INJECTION WITH ADRENALINE 1:200 000 (as bitartrate) ADCO should be used cautiously in areas with limited blood supply, in

the presence of disease that may adversely affect the patient's cardiovascular system or in patients with peripheral vascular disease.

Epidural anaesthesia with any local anaesthetic can cause hypotension and bradycardia which should be anticipated and appropriate precautions taken. These may include preloading the circulation with crystalloid or colloid solution. Epidural anaesthesia, properly performed, is generally well tolerated by obese patients and by those with obstructive lung disease. However, patients with a splinted diaphragm which interferes with breathing, such as those with hydramnios, large ovarian or uterine tumours, pregnancy, ascites or omental obesity are at risk from hypoxia due to respiratory inadequacy and aortocaval compression due to tumour mass. Lateral tilt, oxygen and mechanical ventilation should be used when indicated. Dosage should be reduced in such patients.

Patients who are breathless from any cause e.g. pleural effusion may become hypoxic, especially if the level of anaesthesia is so high as to cause paralysis of the intercostal muscles.

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

For vasoconstrictor-containing preparations such as BUPIVACAINE HCl 0,5 % INJECTION WITH ADRENALINE 1:200 000 (as bitartrate) ADCO, special care should be taken with the following conditions: Asthma, cardiac disease or dysrhythmias, diabetes mellitus, hyperthyroidism, hypertension, peripheral

vascular disease, phaeochromocytoma, narrow angle glaucoma, hypokalaemia, hypercalcaemia, severe renal impairment, prostatic adenoma leading to residual urine, cerebrovascular disease, organic brain damage or arteriosclerosis, in elderly patients, in patients with shock (other than anaphylactic shock) and in organic heart disease or cardiac dilatation.

Adrenaline should be used cautiously, if at all, during general anaesthesia with halogenated hydrocarbon anaesthetics (see section 4.5).

BUPIVACAINE HCl 0,5 % INJECTION WITH ADRENALINE 1:200 000 (as bitartrate) ADCO contains sodium metabisulphite

This may cause allergic-type reactions including anaphylaxis and life threatening or less severe asthmatic episodes in certain susceptible individuals.

Paediatric population

The safety and efficacy of BUPIVACAINE HCl 0,5 % INJECTION WITH ADRENALINE 1:200 000 (as bitartrate) ADCO in children aged under the age of 12 years have not been established.

For epidural anaesthesia children should be given incremental doses commensurate with their age and weight as especially epidural anaesthesia at a thoracic level may result in severe hypotension and respiratory impairment.

4.5 Interaction with other medicines and other forms of interaction

Bupivacaine 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) and mexiletine, since systemic toxic effects are additive.

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).

Adrenaline should not be administered concomitantly with other sympathomimetic medicines because of the possibility of additive effects and increased toxicity.

Alpha-blockers, such as phentolamine, antagonise the vasoconstrictor and hypertensive effects of adrenaline. This effect may be beneficial in adrenaline overdose (see section 4.9).

There is an increased risk of myocardial depression when bupivacaine and antidysrhythmics are given together. Beta blockers such as propranolol reduce the clearance of bupivacaine and may increase bupivacaine toxicity. Severe hypertension and reflex bradycardia may occur with non-cardioselective beta blocking medicines such as propranolol, due to alpha-mediated vasoconstriction. Beta blockers, especially non-cardioselective medicines, also antagonise the cardiac and bronchodilator effects of adrenaline.

Concomitant use of halothane may cause increased cardiotoxicity of bupivacaine.

Administration of adrenaline in patients receiving halogenated hydrocarbon general anaesthetics that increase cardiac irritability and seem to sensitise the myocardium to adrenaline may result in dysrhythmias including ventricular premature contractions, tachycardia or fibrillation (see section 4.4).

Adrenaline specifically reverses the antihypertensive effects of adrenergic neurone blockers such as guanethidine, with the risk of severe hypertension. Adrenaline increases blood pressure and may antagonise the effects of antihypertensive medicines.

Tricyclic antidepressants such as imipramine inhibit reuptake of directly acting sympathomimetic medicines, and may potentiate the effect of adrenaline, increasing the risk of development of hypertension and cardiac dysrhythmias. Although monoamine oxidase (MAO) is one of the enzymes responsible for adrenaline metabolism, MAO inhibitors do not markedly potentiate the effects of adrenaline.

Phenothiazines block alpha-adrenergic receptors.

Adrenaline should not be used in patients receiving high dosage of other medicines (e.g. cardiac glycosides) that can sensitise the heart to dysrhythmias. Some antihistamines (e.g. diphenhydramine) and thyroid hormones may potentiate the effects of adrenaline, especially on heart rhythm and rate. Histamine H_2-antagonists such as cimetidine may decrease clearance of bupivacaine.

Solutions containing adrenaline should also be used with caution in patients receiving dopaminergics such as entacapone, the respiratory stimulant doxapram and the interotropic hormone oxytocin.

The hypokalaemic effect of adrenaline may be potentiated by other medicines that cause potassium loss, including corticosteroids, potassium-depleting diuretics, aminophylline and theophylline. Hypokalaemia may result in increased susceptibility to cardiac dysrhythmias caused by digoxin and other cardiac glycosides.

Adrenaline-induced hyperglycaemia may lead to loss of blood-sugar control in diabetic patients treated with insulin or oral hypoglycaemic medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safe use of BUPIVACAINE HCl 0,5 % INJECTION WITH ADRENALINE 1:200 000 (as bitartrate) ADCO in pregnant women, other than those in labour, has not been established.

Bupivacaine should not therefore be given in early pregnancy unless the benefits are considered to outweigh the risks.

The addition of adrenaline may potentially decrease uterine blood flow and contractility, especially after inadvertent injection into maternal blood vessels.

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. Until further clinical experience is gained, paracervical block with BUPIVACAINE HCl 0,5 % INJECTION WITH ADRENALINE 1:200 000 (as bitartrate) ADCO is not recommended.

Labour may be prolonged leading to the need for caesarean section.

Breastfeeding

Bupivacaine is distributed into breast milk in small amounts.

Fertility

No data on male and female fertility is available.

4.7 Effects on ability to drive and use machines

In general, it is sufficient to allow 2 – 4 hours post-nerve block or until full functions have returned following regional nerve block. In many situations, patients receive sedative or other CNS depressant medicines e.g. diazepam, midazolam to allow the block to be performed.

4.8 Undesirable effects

a. Summary of the safety profile

Reactions to BUPIVACAINE HCl 0,5 % INJECTION WITH ADRENALINE 1:200 000 (as bitartrate) ADCO are characteristic of those associated with other amide-

type local anaesthetics. High plasma levels caused by excessive dosage, inadvertent intravascular injection or slow metabolic degradation, cause systemic reactions involving the central nervous system and the cardiovascular system.

b. Tabulated list of adverse reactions

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Less frequent	Anaemia, methaemoglobinaemia
Immune system disorders	Frequency unknown	Allergic effects are characterised by cutaneous lesions (e.g. urticaria), oedema and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value
Nervous system disorders	Frequent	Paraesthesia, dizziness

	Less frequent	Drowsiness, headache, faecal/urinary incontinence, paralysis of legs, paraesthesias. persistent anaesthesia, respiratory paralysis, restlessness, seizures, trismus of facial muscles, unconsciousness. Signs and symptoms of CNS toxicity (convulsions, circumoral paraesthesia, numbness of the tongue, hyperacusis, visual disturbances, loss of consciousness, tremor, light headedness, tinnitus, dysarthria, muscle twitching)

	Frequency unknown	Excitation or depression: The first manifestation may be nervousness, dizziness, blurred vision or tremors, followed by drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other effects may be chills, constriction of the pupils or tinnitus
Eye disorders	Less frequent	Diplopia
Cardiac disorders	Less frequent	Cardiac dysrhythmias, chest pain, tachycardia, bradycardia
	Frequency unknown	Depression of the myocardium and cardiac arrest
Vascular disorders	Frequent	Hypotension
	Less frequent	Dizziness, hypertension, peripheral vasodilation

Respiratory, thoracic and mediastinal disorders	Less frequent	Respiratory depression
Gastrointestinal disorders	Less frequent	Constipation, nausea and/or vomiting, prolonged numbness of lips and mouth
Skin and subcutaneous tissue disorders	Less frequent	Hives, pruritus, skin rash
Musculoskeletal and connective tissue disorders	Less frequent	Back pain
Renal and urinary disorders	Frequent	Urinary retention
Reproductive system and breast disorders	Less frequent	Impotence
General disorders and administration site conditions	Less frequent	Fever, hypothermia

c. Description of selected adverse reactions

Following epidural injection of some local anaesthetic medicines including bupivacaine, high sympathetic blockade may occasionally result in ocular and other symptoms similar to those seen in Horner's syndrome. These effects are encountered more commonly in pregnant women.

c. Paediatric population

Adverse medicine 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

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc-org) found on SAHPRA website.

For reporting of side effects directly to the Holder of the Certificate of Registration, contact +27 11 635 0134 or email Adcock.aereports@adcock.com

4.9 Overdose

Toxic effects of local anaesthetics require symptomatic treatment; there is no specific cure. The medical practitioner should be prepared to maintain an airway and to support ventilation with oxygen. Supportive treatment of the cardiovascular system includes intravenous fluids and when appropriate, vasopressors. Convulsions may be controlled with oxygen and intravenous administration of diazepam or short-acting barbiturates.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.4 Local anaesthetics

Pharmacotherapeutic group and ATC code: Anaesthetics, local; amides.

ATC code: N01BB51.

Mechanism of action

Administration of BUPIVACAINE HCl 0,5% INJECTION WITH ADRENALINE 1:200 000 (as bitartrate) ADCO stabilises the neuronal membrane and prevents initiation and transmission of nerve impulses, thereby effecting local anaesthetic action. The onset of action is rapid and anaesthesia may last several hours.

Pharmacodynamic effects

Bupivacaine hydrochloride is an amide local anaesthetic which acts at the cell membrane to prevent the generation and the conduction of nerve impulses. Local anaesthetics block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na^+ that is normally produced by a slight depolarisation of the membrane. This action of local anaesthetics is due to their direct interaction with voltage-gated Na^+ channels. As the anaesthetic action progressively develops in a nerve, the threshold for electrical excitability gradually increases, the rate of rise of the action potential declines, impulse conduction slows, and the safety factor for conduction decreases.

The chief vascular action of adrenaline bitartrate is exerted on the smaller arterioles and precapillary sphincters, although veins and large arteries also respond to the medicine. Various vascular beds react differently, which results in a

substantial redistribution of blood flow. Injected adrenaline markedly decreases cutaneous blood flow, constricting precapillary vessels and small venules.

In clinical practice, a vasoconstrictor, usually adrenaline, is often added to local anaesthetics. The vasoconstrictor performs a dual service. By decreasing the rate of absorption, it not only localises the anaesthetic at the desired site, but also allows for the rate at which it is destroyed in the body to keep pace with the rate at which it is absorbed into circulation. This reduces its systemic toxicity.

5.2 Pharmacokinetic properties

Distribution

Redistribution of bupivacaine is dependent on its tissue partition coefficient and the mass and perfusion of the tissue.

The amount of free medicine is dependent on its binding to tissue and erythrocyte proteins, its non-specific binding to albumin and specific binding to alpha lipoproteins in the plasma and the pH gradient.

Biotransformation

Because of its amide structure, bupivacaine is not detoxified by plasma esterases. When administered in recommended doses and concentration, it does not ordinarily produce irritation or tissue damage and does not cause methaemoglobinaemia.

Elimination

It is cleared from the body by metabolism and excretion.

Paediatric population

In children the pharmacokinetics is similar to that in adults.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ascorbic acid, edetate calcium disodium, monothioglycerol, sodium chloride, sodium metabisulphate, sodium lactate solution, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), water for injection.

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must 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 pack of 2 shrink-wrapped cartons, each containing 5 x 20 mL clear, one-point cut (OPC) glass ampoules.

The ampoules are packed into a white EPS tray box.

6.6 Special precautions for disposal and other handling

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

Discard unused portion after initial use.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

51/4/0548

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 January 2022

10 DATE OF REVISION OF THE TEXT

11 August 2025