PROFESSIONAL INFORMATION

SCHEDULING STATUS **S4**

1 NAME OF THE MEDICINE

MACAINE HCl 0,5 % INJECTION

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL sterile aqueous solution contains bupivacaine hydrochloride 5 mg

Sugar free

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Injection

Clear, colourless, aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Peripheral nerve block, caudal or epidural block.

4.2 Posology and method of administration

Posology

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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, MACAINE 0,5 % HCl 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 MACAINE 0,5 % HCl 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.		

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Caudal anaesthesia	15 – 30	75 – 150	

The maximum recommended dose of MACAINE 0,5 % HCl 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.

Elderly

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

Paediatric population

MACAINE 0,5 % HCl 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.

Check plastic ampoules for minute leaks by squeezing.

Do not use if solution is brown or contains a precipitate. Discard unused portion after initial use.

4.3 Contraindications

- MACAINE 0,5 % HCl is contra-indicated in patients with known sensitivity to bupivacaine or to any of the excipients listed in 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
- Paracervical block (see section 4.4)
- MACAINE 0,5 % HCl is not recommended for children younger than 12 years.
- Safe use in pregnancy and lactation, other than for use in labour, has not been established (see section 4.6).

4.4 Special warnings and precautions for use

RESUSCITATIVE EQUIPMENT AND [~~DRUGS~~] MEDICINES SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANAESTHETIC IS USED.

Before any nerve block is attempted, intravenous access for resuscitation purposes should be established. Healthcare professionals should have received adequate and appropriate training in the procedure to be performed and should

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be familiar with the diagnosis and treatment of side effects, systemic toxicity or other complications (see section 4.9).

Foetal bradycardia frequently follows paracervical block with some amide-type local anaesthetics, such as MACAINE 0,5 % HCl 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 MACAINE 0,5 % HCl is not recommended.

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

MACAINE 0,5 % HCl 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 MACAINE 0,5 % HCl 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 MACAINE 0,5 % HCl and antidysrhythmic 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 MACAINE 0,5 % HCl 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 postoperative intra-articular continuous infusion of local anaesthetics. The majority of reported cases of chondrolysis have

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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 MACAINE 0,5 % HCl.

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

Epidural anaesthesia with MACAINE 0,5 % HCl 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.

When administering repeat doses of MACAINE 0,5 % HCl, precaution should be taken with patients with severe liver disease. If signs of hepatic dysfunction are observed during the treatment with MACAINE 0,5 % HCl, the medicine should be discontinued.

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

MACAINE 0,5 % HCl contains sodium:

MACAINE 0,5 % HCl contains 8,00 mg sodium per mL, equivalent to 0,4 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric population

MACAINE 0,5 % HCl is not recommended for children younger than 12 years.

4.5 Interaction with other medicines and other forms of interaction

MACAINE 0,5 % HCl 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.
Specific interaction studies with MACAINE 0,5 % HCl 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 MACAINE 0,5 % HCl. There is a risk of increased bupivacaine toxicity when these medicines are used concomitantly.

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

Interactions between MACAINE 0,5 % HCl 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

Safety in pregnancy and lactation, other for use in labour, has not been established.

Breastfeeding

Bupivacaine, the active ingredient of MACAINE 0,5 % HCl, 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, MACAINE 0,5 % HCl 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

Reactions to MACAINE 0,5 % HCl 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
Immune system disorders	Uncommon	Allergic reactions, anaphylactic reactions/shock
Psychiatric disorders	Uncommon	Excitation, depression, nervousness
Nervous system disorders	Common	Paraesthesia, dizziness
	Uncommon	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	Uncommon	Constriction of the pupils, diplopia, blurred vision
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Common	Bradycardia

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	Uncommon	Myocardial depression, arrhythmia, cardiac arrest, oedema, ventricular dysrhythmias
Vascular disorders	Common	Changes in blood pressure (usually hypotension), hypertension
Respiratory, thoracic and mediastinal disorders	Uncommon	Respiratory depression
Gastrointestinal disorders	Common	Nausea, vomiting
Hepatobiliary disorders	Uncommon	Hepatic dysfunction, with reversible increase of liver enzymes and bilirubin
Skin and subcutaneous tissue disorders	Uncommon	Pruritus, urticaria, skin rash
Renal and urinary disorders	Common	Urinary retention
General disorders and administration site conditions	Uncommon	Skin or intravenous reaction may occur at the site of injection if the patient shows sensitivity to MACAINE 0,5 % HCl.

		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 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,

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hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

Recovery is due to redistribution of the local anaesthetic 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 as in MACAINE 0,5 % HCl 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 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

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

Toxic effects of local anaesthetics require symptomatic treatment; there is no specific cure.

The physician 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: N01BB01.

Administration of bupivacaine 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. The duration of action is significantly longer with MACAINE 0,5 % HCl than with any other commonly used local anaesthetic.

When administered in recommended doses and concentration, it does not ordinarily produce irritation or tissue damage and does not cause methaemoglobinaemia.

5.2 Pharmacokinetic properties

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Because of its amide structure, bupivacaine is not detoxified by plasma esterases.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, sodium hydroxide (pH adjuster), hydrochloric acid (pH adjuster) and water for injections.

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.

Discard unused portion after initial use.

6.5 Nature and contents of container

A 10 mL single dose, clear neutral glass (USP Type 1) ampoule, or

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A single dose, semi-rigid, transparent, low density polyethylene (LDPE) plastic ampoule.

Ten ampoules are packed in an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

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Date of registration: 28 June 1976

10 DATE OF REVISION OF THE TEXT

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