

Marcaine 0.5% Spinal Heavy (5 mg/mL)*bupivacaine***Solution for spinal injection****Composition***Active constituents*

Marcaine Spinal Heavy 5mg/mL: 1 mL contains: bupivacaine hydrochloride 5 mg.

For excipients, see List of excipients.

Pharmaceutical form

Solution for injection

Therapeutic indications

Marcaine Spinal Heavy is indicated for intrathecal (subarachnoid, spinal) anaesthesia for surgical and obstetrical procedures.

Marcaine Spinal Heavy is indicated for lower abdominal surgery (including Caesarean section), urological and lower limb , including hip surgery lasting 1.5-3 hours (see also Posology and method of administration).

Posology and method of administration*Adults*

The following dosage recommendations is a guide for the more commonly used techniques in the average adult.

The clinician's experience and knowledge of the patient's physical status are of importance in calculating the required dose. The lowest dose required for adequate anaesthesia should be used. Duration varies with dose, while segmental spread may be difficult to predict, especially with the isobaric (plain) solution.

The dose should be reduced in the elderly and in patients in the late stages of pregnancy.

Dosage recommendations	Conc. mg/mL	Dose		Onset (min)	Duration (h)
		mL	mg		
Marcaine Spinal Heavy					

Dosage recommendations	Conc. mg/mL	Dose		Onset (min)	Duration (h)
		mL	mg		
Urological	5.0	1.5-3	7.5-15	5-8	2-3
Lower abdominal surgery (incl. Caesarean section), lower limb, including hip surgery	5.0	2-4	10-20	5-8	1.5-3

The recommended injection site is the L₃-L₄ intervertebral space.

Children up to 40 kg

Marcaïne Spinal Heavy may be used in children.

One of the differences between small children and adults is a relatively high CSF volume in infants and neonates, requiring a relatively larger dose/kg to produce the same level of block as compared to adults.

Dosage recommendations in children

Body weight (kg)	Dose (mg/kg)
<5	0.40-0.50 mg/kg
5 to 15	0.30-0.40 mg/kg
15 to 40	0.25-0.30 mg/kg

Contraindications

Hypersensitivity to local anaesthetics of the amide type or to any of the excipients.

General contraindications related to intrathecal anaesthesia should be taken into account:

- Acute active disease of the central nervous system, such as meningitis, tumours, poliomyelitis and cranial haemorrhage.
- Spinal stenosis and active disease (e.g. spondylitis, tumour) or recent trauma (e.g. fracture) in the vertebral column.
- Septicaemia.
- Pernicious anaemia with subacute combined degeneration of the spinal cord.
- Pyogenic infection of the skin at or adjacent to the site of puncture.

- Cardiogenic or hypovolaemic shock.
- Coagulation disorders or ongoing anticoagulant treatment.

Special warnings and precautions for use

Intrathecal anaesthesia should only be undertaken by or under the supervision of clinicians with the necessary knowledge and experience

Regional anaesthetic procedures should always be performed in a properly equipped and staffed area with equipment and drugs necessary for monitoring and emergency resuscitation immediately available.

Intravenous access, e.g. an i.v. infusion, should be in place **before** starting the intrathecal anaesthesia.

Clinicians 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 Overdose).

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. Patients treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive (see Interaction).

Like all local anaesthetic drugs, 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 drug. This is especially the case after unintentional intravascular administration. Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported in connection with high systemic concentrations of bupivacaine. However, high systemic concentrations are not expected with doses normally used for intrathecal anaesthesia.

Intrathecal anaesthesia may lead to hypotension and bradycardia. The risk of such effects can be reduced, e.g., by injecting a vasopressor. Hypotension should be treated promptly with a sympathomimetic intravenously, repeated as necessary.

A rare, though severe, adverse reaction following spinal anaesthesia is high or total spinal blockade resulting in cardiovascular and respiratory depression. The cardiovascular depression is caused by extensive sympathetic blockade which may result in profound hypotension and bradycardia, or even cardiac arrest. Respiratory depression may be caused by blockade of the innervation of the respiratory muscles, including the diaphragm.

There is an increased risk for high or total spinal blockade in the elderly and in patients in the late stages of pregnancy. The dose should therefore be reduced in these patients (see also Posology and method of administration).

Patients with hypovolaemia can develop sudden and severe hypotension during intrathecal anaesthesia, regardless of the local anaesthetic used. The hypotension usually seen after intrathecal blocks in adults is uncommon in children under the age of 8.

Neurological injury is a rare consequence of intrathecal anaesthesia and may result in paraesthesia, anaesthesia, motor weakness and paralysis. Occasionally these are permanent.

Neurological disorders, such as multiple sclerosis, haemiplegia, paraplegia and neuromuscular disorders are not thought to be adversely affected by intrathecal anaesthesia, but call for caution. Before treatment is instituted, consideration should be taken if the benefits outweigh the possible risks for the patient.

Interactions

Bupivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics e.g. certain anti-arrhythmics, such as lidocaine and mexiletine, since the systemic toxic effects are additive. Specific interaction studies with bupivacaine and anti-arrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution should be advised (see also Special warnings and special precautions for use).

Pregnancy and lactation

Pregnancy

It is reasonable to assume that a large number of pregnant women and women of child-bearing age have been given bupivacaine. No specific disturbances to the reproductive process have so far been reported, e.g. no increased incidence of malformations (see Pharmacokinetic properties). It should be noted that the dose should be reduced in patients in the late stages of pregnancy (see also Posology and method of administration).

Lactation

Bupivacaine enters the mother's milk, but in such small amounts that there is generally no risk of this affecting the neonate.

Effects on ability to drive and use machines

Besides the direct anaesthetic effect, local anaesthetics may have a very mild effect on mental function and coordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.

Undesirable effects

The adverse reaction profile for Marcaine Spinal Heavy is similar to those for other long acting local anaesthetics administered intrathecally. Adverse reactions caused by the drug *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 the needle puncture or events associated to cerebrospinal leakage (e.g. postdural puncture headache).

Table of Adverse Drug Reactions

Very Common (> 1/10)	<i>Cardiac disorders:</i> Hypotension, bradycardia <i>Gastrointestinal disorders:</i> Nausea
Common (>1/100 <1/10)	<i>Nervous system disorders:</i> Postdural puncture headache <i>Gastrointestinal disorders:</i> Vomiting <i>Renal and urinary disorders:</i> Urinary retention, urinary incontinence
Uncommon (>1/1,000 <1/100)	<i>Nervous system disorders:</i> Paraesthesia, paresis, dysaesthesia <i>Musculoskeletal, connective tissue and bone disorders:</i> Muscle weakness, back pain
Rare (<1/1,000)	<i>Cardiac disorders:</i> Cardiac arrest <i>Immune system disorders:</i> Allergic reactions, anaphylactic shock <i>Nervous system disorders:</i> Total spinal block unintentional, paraplegia, paralysis, neuropathy, arachnoiditis <i>Respiratory disorders:</i> Respiratory depression

Overdose

Acute systemic toxicity

Marcaine Spinal Heavy 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.

Treatment of acute systemic toxicity

If signs of acute systemic toxicity or total spinal block appear, injection of the local anaesthetic should be stopped immediately and cardiovascular and neurological symptoms (convulsions, CNS depression) must be treated adequately.

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.

If cardiovascular depression is evident (hypotension, bradycardia), ephedrine 5-10 mg i.v. should be given and this dose should be repeated, if necessary, after 2-3 minutes. Children should be given ephedrine doses commensurate with their age and weight.

If convulsions due to systemic toxicity occurs, the objective of treatment is to maintain oxygenation, stop the convulsions and support the circulation. Oxygen must be given and ventilation assisted, when necessary (mask and bag or tracheal intubation). An anticonvulsant should be given i.v. if the convulsions do not stop spontaneously in 15-20 seconds. Thiopentone sodium 1-3 mg/kg i.v. will abort the convulsions rapidly. Alternatively diazepam 0.1 mg/kg i.v. may be used, although its action will be slow. Prolonged convulsions may jeopardize the patient's ventilation and oxygenation. If so, injection of a muscle relaxant (e.g. succinylcholine 1 mg/kg) will rapidly stop the convulsions so that ventilation and oxygenation can be controlled. Endotracheal intubation must be considered in such situations.

Pharmacodynamic properties

Pharmacotherapeutic group (ATC code): N01B B01

Bupivacaine is a local anaesthetic of the amide type. Given as an intrathecal anaesthetic it has a rapid onset and a medium to long duration. The duration is dose-dependent.

Bupivacaine, like other local anaesthetics, causes a reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the nerve membrane.

Marcaïne Spinal Heavy is hyperbaric and its initial spread in the intrathecal space is affected by gravity. Due to the small dose the intrathecal distribution results in a relatively low concentration and the duration of the local anaesthetic tends to be relatively short.

Plain solutions (without dextrose) produce a less predictable level of block, but of longer duration, than the hyperbaric solutions.

Pharmacokinetic properties

Bupivacaine has a pKa of 8.2 and a partition coefficient of 346 (25°C n-octanol/ phosphate buffer pH 7.4). The metabolites have a pharmacological activity that is less than that of bupivacaine.

Bupivacaine shows complete and biphasic absorption from the subarachnoid space with half-lives of the two phases of the order of 50 and 408 minutes. The slow absorption phase is the rate-limiting factor in the elimination of bupivacaine, which explains why the apparent terminal half-life is longer after subarachnoidal administration than after intravenous administration. The blood concentration of bupivacaine after intrathecal block is low compared with those after other regional anaesthetic procedures, due to the small dose required for intrathecal anaesthesia. Generally, the increment in maximum plasma concentration is approximately 0.4 mg/L for every 100 mg injected. This means that a dose of 20 mg would result in plasma levels in the order of 0.1 mg/L.

After i.v. injection bupivacaine has a total plasma clearance of 0.58 L/min, a volume of distribution at steady state of 73 L, a terminal half-life of 2.7 h and an intermediate hepatic extraction ratio of 0.38 after i.v. administration. It is mainly bound to alpha-1-acid glycoprotein in plasma with a plasma binding of 96%. Clearance of bupivacaine is almost entirely due to liver metabolism, and more sensitive to changes in intrinsic hepatic enzyme function than to liver perfusion.

Bupivacaine readily crosses the placenta and equilibrium with regard to the unbound concentration is rapidly reached. The degree of plasma protein binding in the foetus is less than in the mother, which results in lower total plasma concentrations in the foetus.

Bupivacaine is excreted in breast milk, but in such small quantities that there is no risk to the child.

Bupivacaine is extensively metabolized in the liver, predominately by aromatic hydroxylation to 4-hydroxy-bupivacaine and N-dealkylation to PPX, both mediated by cytochrome P4503A4. About 1% of bupivacaine is excreted in the urine as unchanged drug in 24 h and approximately 5% as PPX. The plasma concentrations of PPX and 4-hydroxy-bupivacaine during and after continuous administration of bupivacaine are low as compared to the parent drug.

Preclinical safety data

Based on conventional studies with bupivacaine of safety pharmacology, single and repeated dose toxicity, reproduction toxicity, mutagenic potential and local toxicity, no hazards for humans were identified other than those which can be expected on the basis of the pharmacodynamic action of high doses of bupivacaine (e.g. CNS signs and cardiotoxicity.)

List of excipients

Dextrose monohydrate, 80.0 mg

Sodium hydroxide and/or hydrochloric acid for pH adjustment to 4.0-6.0

Water for injections to 1 mL

The relative density of the solution is 1.026 at 20°C (corresponding to 1.021 at 37°C).

Incompatibilities

Additions to spinal solutions are not generally recommended.

Shelf-life

Please see outer pack.

Special precautions for storage

Do not store above 25°C. Do not freeze.

Pack size

Please see outer pack.

Nature and contents of container

Marcaine Spinal Heavy is supplied in type I glass ampoules with/without blister.

Instructions for use/handling

Marcaine Spinal Heavy is free from preservative and intended for single use only. Any remaining solution should be discarded.

Since Marcaine Spinal Heavy contains glucose, caramelization may occur during autoclaving. This preparation should therefore not be re-sterilized.

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