

1. NAME OF THE MEDICINAL PRODUCT

Marcaïn Heavy Steripack, 0.5%w/v Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains Bupivacaine Hydrochloride equivalent to 5.0 mg of anhydrous bupivacaine hydrochloride (20 mg per 4 ml ampoule).

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless, sterile aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intrathecal spinal anaesthesia in adults and children of all ages.

4.2 Posology and method of administration

Posology

Adults and children above 12 years of age

The following table is a guide to dosage for the more commonly used techniques in the average adult. The figures reflect the expected average dose range needed. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

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. Individual variations in onset and duration occur, and the extent of the spread of anaesthesia may be difficult to predict, but will be affected by the volume of the drug used.

Dosage recommendations

	Conc. mg/ml	Dose		Onset (min)	Duration (h)
		ml	mg		
Urological	5	1.5–3	7.5–15	5–8	2–3
Lower abdominal surgery (incl. caesarean section), lower limb, including hip surgery	5	2–4	10–20	5–8	1.5–3

Pregnant women: 2–2.5 ml (10–12.5 mg bupivacaine hydrochloride).

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

Neonates, infants and children up to 40 kg

Marcaïn 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.

Paediatric regional anaesthesia procedures should be performed by qualified clinicians who are familiar with this population and the techniques.

The doses in the table should be regarded as guidelines for use in paediatric patients. Individual variations occur. Standard textbooks should be consulted for factors affecting specific block technique and for individual patient requirements. The lowest dose required for adequate anaesthesia should be used.

Dosage recommendations in neonates, infants and 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

The spread of anaesthesia obtained with Marcaïn Heavy, depends on several factors including the volume of solution and the position of the patient during and following the injection.

When injected at the L₃–L₄ intervertebral space, with the patient in the sitting position, 3 ml of Marcaïn Heavy usually spreads to the T₇–T₁₀ spinal segments. With the patient receiving the injection in the horizontal position and then turned

supine, the blockade spreads to T₄–T₇ spinal segments. It should be understood that the level of spinal anaesthesia achieved with any local anaesthetic can be unpredictable in a given patient.

The recommended site of injection is below L3.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to local anaesthetics of the amide type.

Bupivacaine should not be injected into inflamed or infected areas.

Intrathecal 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, sub-acute combined degeneration of the cord due to pernicious anaemia and cerebral and spinal tumours.
- Raised intracranial pressure.
- Spinal stenosis and active disease (e.g. spondylitis, tumour, tuberculosis of the spine) or recent trauma (e.g. fracture) in the vertebral column.
- Septicaemia.
- 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

Intrathecal anaesthesia should only be undertaken by clinicians with the necessary knowledge and experience.

Regional anaesthetic procedures should always be performed in a properly equipped and staffed area. Resuscitative equipment and drugs should be immediately available and the anaesthetist should remain in constant attendance.

Intravenous access, e.g. an i.v. infusion, should be in place before starting the intrathecal anaesthesia. The clinician responsible should take the necessary precautions to avoid intravascular injection and be appropriately trained and familiar with the diagnosis and treatment of side effects, systemic toxicity and other

complications. If signs of acute systemic toxicity or total spinal block appear, injection of the local anaesthetic should be stopped immediately, see sections 4.8 and 4.9.

Cardiovascular and respiratory vital signs and the patient's state of consciousness after local anaesthetic injection should be carefully and constantly monitored as sympathetic blockage occurring during spinal anaesthesia may result in peripheral vasodilatation and hypotension. Also, the level of anaesthesia should be carefully monitored because this is not always predictable in spinal techniques.

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 or injection into highly vascular areas. Cardiovascular system toxicity 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.

Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported in connection with high systemic concentrations of bupivacaine. Should cardiac arrest occur, a successful outcome may require prolonged resuscitative efforts. However, high systemic concentrations are not expected with doses normally used for intrathecal anaesthesia.

There is an increased risk of 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 Section 4.2.

Intrathecal anaesthesia with any local anaesthetic 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. 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 intrathecal anaesthesia.

Intrathecal anaesthesia can cause intercostal paralysis and patients with pleural effusions may suffer respiratory embarrassment. Septicaemia can increase the risk of intraspinal abscess formation in the postoperative period.

Before treatment is instituted, consideration should be taken if the benefits outweigh the possible risks for the patient.

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 kept under close surveillance and ECG monitoring considered, since cardiac effects may be additive. (See section 4.5).

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 of 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.

Neurological disorders, such as multiple sclerosis, haemiplegia, paraplegia and neuromuscular disorders are thought not 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.

This medicine contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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 is advised (see also section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

When this product is used for the production of obstetric analgesia, it is essential that the mother be placed on her side or tilted laterally, to avoid caval occlusion, with consequent maternal hypotension and acidosis.

It should be noted that the dose should be reduced in patients in the late stages of pregnancy, see also section 4.2.

Breast-feeding

Bupivacaine enters the mother's milk, but in such small quantities that there is generally 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, local anaesthetics may have a very mild effect on mental function and coordination even in the absence of overt toxicity and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

4.8.1 General

The adverse reaction profile for Marcain Heavy is similar to those of other long-acting local anaesthetics used for intrathecal anaesthesia.

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 needle puncture or events associated to cerebrospinal leakage (e.g. postdural puncture headache).

High spinal anaesthesia may result in paralysis of all respiratory muscles.

Neurological damage is a rare but well recognised consequence of regional and particularly spinal anaesthesia. It may be due to several causes, e.g. direct injury to the spinal cord or spinal nerves, anterior spinal artery syndrome, injection of an irritant substance, or an injection of a non-sterile solution. These may result in localised areas of paraesthesia or anaesthesia, motor weakness, loss of sphincter control and paraplegia. Occasionally these are permanent. Neurological complications of this type have been reported after the use of all local anaesthetics used for spinal anaesthesia.

Tabulated list of adverse reactions

Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) or not known (cannot be estimated from the available data).

Table of Adverse Drug Reactions

System Organ	Frequency Classification	Adverse Drug Reaction
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Class

Immune system disorders	Rare	Allergic reactions, anaphylactic shock
Nervous system disorders	Common	Postdural puncture headache
	Uncommon	Paraesthesia, paresis, dysaesthesia
	Rare	Total unintentional spinal block, paraplegia, paralysis, neuropathy, arachnoiditis
Cardiac disorders	Very Common	Hypotension, bradycardia
	Rare	Cardiac arrest
Respiratory, thoracic and mediastinal disorders	Rare	Respiratory depression
Gastrointestinal disorders	Very Common	Nausea
	Common	Vomiting
Musculoskeletal and connective tissue disorders	Uncommon	Muscle weakness, back pain
Renal and urinary disorders	Common	Urinary retention, urinary incontinence

4.8.2 Acute systemic toxicity

Marcaïn Heavy Steripack, 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.

Systemic toxicity is rarely associated with spinal anaesthesia but might occur after accidental intravascular injection. Systemic adverse reactions are characterised by numbness of the tongue, light-headedness, dizziness and tremors, followed by convulsions and cardiovascular disorders.

4.8.3 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 CNS symptoms (convulsion, CNS depression) must promptly be treated with appropriate airway/respiratory support and the administration of anticonvulsant drugs.

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 occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, and or inotropic agents should be considered. Children should be given doses commensurate with age and weight.

Paediatric population

Adverse drug 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Marcain Heavy Steripack, 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. (See section 4.8.2 and 4.8.3).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC code): N01B B01

Bupivacaine is a long-acting local anaesthetic agent of the amide type. Marcain Heavy produces a moderate muscular relaxation of the lower extremities lasting 2–

2.5 hours. The motor blockade of the abdominal muscles makes the solution suitable for performance of abdominal surgery lasting 45–60 minutes.

The cardiovascular effects of Marcain Heavy are similar or less than those seen with other spinal agents. Bupivacaine 5 mg/ml with glucose 80 mg/ml is exceptionally well tolerated by all tissues with which it comes in contact.

Marcain 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.

5.2 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 plasma 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 iv 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 iv 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 metabolised 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.

Paediatric population

In children the pharmacokinetics are similar to that in adults.

5.3 Preclinical safety data

Bupivacaine hydrochloride is a well-established active ingredient.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Glucose anhydrous

Water for injections

6.2 Incompatibilities

The solution must not be stored in contact with metals, e.g. needles or metal parts of syringes, as dissolved metal ions may cause swelling at the site of the injection.

6.3 Shelf-life

Unopened: 3 years.

Once opened: The solution should be used immediately after opening of the ampoule. Any remaining solution should be discarded.

6.4 Special precautions for storage

Do not store above 25°C. Keep the ampoules in the outer carton.

6.5 Nature and contents of container

5 ml Type I (Ph. Eur.) clear, glass ampoules. Each ampoule contains 4 ml of solution for injection in blisters of 5 ampoules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only. The solution should be used immediately after opening the ampoule. Any remaining solution should be discarded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
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Citywest Business Campus
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBER (S)

PA 1691/024/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

2nd April 1987 / 2nd April 2007

10. DATE OF REVISION OF THE TEXT

August 2022