Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Marcain 0.5% w/v with Adrenaline (Epinephrine, 5 micrograms per ml) (1:200,000) Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains bupivacaine hydrochloride equivalent to anhydrous bupivacaine hydrochloride 5.0 mg per ml (100 mg per 20 ml single dose vial) and Adrenaline Tartrate (epinephrine bitartrate) equivalent to adrenaline (epinephrine) 5 micrograms per ml (100 micrograms per 20 ml single dose vial).
Excipient(s) with known effect: sodium metabisulphite (0.5 mg/ml, equivalent to 10 mg per 20 ml single dose vial), sodium (in total 3.2 mg/ml , equivalent to 64.1 mg per 20 ml single dose vial),
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless, aqueous, sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Marcain 0.5% w/v with Adrenaline is indicated for:
- Surgical anaesthesia in adults and children above 12 years of age
- Acute pain management in adults and children above 12 years of age.

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. For young, elderly or debilitated patients, these doses should be reduced.

Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

N.B. When prolonged blocks are used, either by continuous infusion or by repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing a local neural injury must be considered.

The clinician's experience and knowledge of the patient's physical status is important in calculating the required dose. The lowest dose required for adequate anaesthesia should be used. Individual variations in onset and duration occur. The duration may be prolonged with the adrenaline-containing solutions. (See Table below).

N.B. Risk of systemic effects of adrenaline with large volumes of adrenaline-containing solutions should be considered. Marcaine with adrenaline should not be used for epidural block in labour analgesia (apart from the use as a test dose) as the benefits from the addition of adrenaline have not been shown to outweigh the risks.

Dosage recommendations for adult

	Conc mg/ml	Volume ml	Dose mg	Onset min	Duration of effect hours[g)]
SURGICAL ANAESTHESIA					
Lumbar Epidural Administration[a)]					
Surgery	5	15–30	75–150	15–30	2–3
Caesarean Section	5	15–30	75–150	15–30	2–6
Thoracic Epidural Administration[a)]					
Surgery	2.5	5–15	12.5–37.5	10–15	1.5–2
	5	5–10	25–50	10–15	3–4
Caudal Epidural Block[a)]	2.5	20–30	50–75	20–30	3–4
	5	20–30	100–150	15–30	4–6
Major Nerve Block[b)]					
(e.g. brachial plexus, femoral, sciatic)	5	10–35	50–175	15–30	4–8
Field block					
(e.g. minor nerve blocks and infiltration)	2.5	<60	<150	1–3	3–4
	5	≤ 30	≤ 150	1–10	3–8
ACUTE PAIN MANAGEMENT					
Lumbar Epidural Administration					
Intermittent injections[c), h)] (post-operative pain relief)	2.5	6–15 (Minimum interval 30 minutes)	15–37.5 (Minimum interval 30 minutes)	2–5	1–2
Continuous infusion[d), h)]	2.5	5–7.5/h	12.5–18.8/h	–	–
Thoracic Epidural Administration					
Continuous infusion[d)]	2.5	4–7.5/h	10–18.8/h	–	–
Intra-Articular Block[f)]					
(e.g. single injection following knee arthroscopy)	2.5	≤40	≤100[e)]	5–10	2–4 h after wash out
Field Block					
(e.g. minor nerve blocks and infiltration)	2.5	≤60	≤150	1–3	3–4

a) Dose includes test dose.

b) The dose for a major nerve block must be adjusted according to site of administration and patient status. Interscalene and supraclavicular brachial plexus blocks may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used, see also section 4.4.

c) In total ≤400 mg/24 h.

d) This solution is often used for epidural administration in combination with a suitable opioid for pain management. In total ≤400 mg/24 h.

e) If additional bupivacaine is used by any other techniques in the same patient, an overall dose limit of 150 mg should not be exceeded.

f) There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics. Marcain is not approved for this indication (see also section 4.4).

g) Marcain with adrenaline.

h) Marcaine with adrenaline should not be used for epidural block in labour analgesia (apart from the use as a test dose) as the benefits from the addition of adrenaline have not been shown to outweigh the risks.

In general, surgical anaesthesia (e.g. epidural administration) requires the use of higher concentrations and doses. When a less intense block is required, the use of a lower concentration is indicated. The volume of drug used will affect the extent of spread of anaesthesia.

In order to avoid intravascular injection, aspiration should be repeated prior to and during administration of the main dose, which should be injected slowly or in incremental doses, at a rate of 25–50 mg/min, while closely observing the patient's vital functions and maintaining verbal contact. When an epidural dose is to be injected, a preceding test dose of 3–5 ml bupivacaine containing adrenaline is recommended. An inadvertent intravascular injection may be recognised by a temporary increase in heart rate and an accidental intrathecal injection by signs of a spinal block. If toxic symptoms occur, the injection should be stopped immediately. (See section 4.8.1).

Experience to date indicates that 400 mg administered over 24 hours is well tolerated in the average adult.

Paediatric population 1 to 12 years of age

The safety and efficacy of Marcain 0.5% w/v with Adrenaline in children aged <12 years has not been established. Only limited data are available. Marcain 0.25% w/v with Adrenaline may be more appropriate for administration to children aged 1-12 years.

4.3 Contraindications

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

Bupivacaine hydrochloride solutions are contraindicated in patients with hypersensitivity to local anaesthetic agents of the amide type.

Hypersensitivity to sodium metabisulphite in solutions containing adrenaline.

Solutions of bupivacaine hydrochloride with adrenaline should not be used in connection with anaesthesia in areas of the body supplied by end arteries (e.g. penile block, Oberst block) as it may cause ischemic tissue necrosis or otherwise having a compromised blood supply such as digits, nose, external ear, penis, etc., or in spinal anaesthesia because of the adrenaline content; plain solutions must be used for this purpose.

Solutions of bupivacaine hydrochloride are contraindicated for intravenous regional anaesthesia (Bier's-block) and for injection into inflamed or infected areas.

Use in paracervical block in obstetrics.

Solutions containing adrenaline are contraindicated in patients with thyrotoxicosis or severe heart disease, particularly when tachycardia is present.

4.4 Special warnings and precautions for use

There have been reports of cardiac arrest or death during use of bupivacaine for epidural anaesthesia or peripheral nerve blockade. In some instances, resuscitation has been difficult or impossible despite apparently adequate preparation and management.

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. Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported in connection with high systemic concentrations of bupivacaine.

Regional or local anaesthetic procedures should always be performed in a properly equipped and staffed area. Equipment and drugs 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 i.v. line inserted before the blocking procedure. The clinician responsible should take the necessary precautions to avoid overdose or intravascular injection, always including careful aspiration (see section 4.2), 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 (see sections 4.8 & 4.9).

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.

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 elderly and patients in poor general condition.
- 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.
- 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.

Certain local anaesthetic procedures may be associated with serious adverse reactions, regardless of the local anaesthetic drug used:

- Central nerve blocks may cause cardiovascular depression, especially in the presence of hypovolaemia. Epidural anaesthesia should be used with caution in patients with impaired cardiovascular function.
- Retrobulbar injections may very occasionally reach the cranial subarachnoid space causing temporary blindness, cardiovascular collapse, apnoea, convulsions etc.
- 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.
- Injections in the head and neck regions made inadvertently into an artery which may cause immediate cerebral symptoms even at low doses.
- Paracervical block can sometimes cause foetal bradycardia/tachycardia, and careful monitoring of the foetal heart rate is necessary.
- 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 Marcain.

Epidural 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.

The lowest dose that produces effective anaesthesia should be used. Injection of repeated doses of bupivacaine hydrochloride may cause significant increases in blood levels with each repeated dose due to slow accumulation of the drug. Tolerance varies with the status of the patient. Debilitated, elderly or acutely ill patients should be given reduced doses commensurate with their physical status. The continuous or repeated administration of this product may give rise to cumulative toxicity and tachyphylaxis (see section 4.8).

Bupivacaine hydrochloride should be used with caution in patients with epilepsy, impaired cardiac conduction or in those with hepatic or renal damage.

Marcain solutions should be used with caution in persons with known drug sensitivities. Patients allergic to ester-type local anaesthetic drugs (procaine, tetracaine, benzocaine, etc) have not shown cross-sensitivity to agents of the amide type such as bupivacaine.

Since bupivacaine is metabolised in the liver, it should be used cautiously in patients with liver disease or with reduced liver blood flow (e.g. in severe shock).

Paediatric population

The safety and efficacy of Marcain 0.5% w/v with Adrenaline in children aged < 12 years has 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.

When bupivacaine is administered as an intra-articular injection, caution is advised when recent major intra-articular trauma is suspected or extensive raw surfaces within the joint have been created by the surgical procedure, as that may accelerate absorption and result in higher plasma concentrations.

Solutions containing adrenaline should be used with caution for patients whose medical history and physical evaluation suggest the existence of hypertension, arteriosclerotic heart disease, cerebrovascular insufficiency, heart block, thyrotoxicosis, diabetes or any other pathological condition that might be aggravated by the effects of adrenaline.

Serious cardiac arrhythmias may occur if preparations containing a vasoconstrictor drug are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichlorethylene or other related agents.

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

Solutions containing a vasopressor if used in caudal, epidural or paracervical block during labour may reduce uterine and spinal blood flow together with uterine contractility, and may also give rise to serious systemic effects in pre-eclampsia or where an oxytoxic drug is used post-partum.

This medicinal product contains 64.1 mg sodium per vial, equivalent to 3.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
Also contains sodium metabisulphite. This may rarely cause severe hypersensitivity reactions and bronchospasm.

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 section 4.4).

Solutions containing adrenaline should be used with caution in those patients receiving drugs known to produce blood pressure alterations, i.e. MAO inhibitors, tricyclic antidepressants, phenothiazines, etc., as severe and sustained hypotension or hypertension may occur. The concurrent use of adrenaline-containing solutions and oxytocic drugs of the ergot type may cause severe, persistent hypertension and possibly cerebrovascular and cardiac accidents. Neuroleptics such as phenothiazines may oppose the vasoconstrictor effects of adrenaline giving rise to hypotensive responses and tachycardia.

Solutions containing adrenaline should be used with caution in patients undergoing general anaesthesia with inhalation agents such as halothane and enflurane, due to the risk of serious cardiac arrhythmias. Suitable beta-blockers should be immediately available and both hypoxia and hypercapnia should be avoided.

Non-selective beta-blockers such as propranolol enhance the pressor effects of adrenaline, which may lead to severe hypertension and bradycardia.

4.6 Fertility, pregnancy and lactation

Pregnancy
Foetal adverse effects due to local anaesthetics, such as foetal bradycardia, seem to be most apparent in paracervical block anaesthesia. Such effects may be due to high concentrations of anaesthetic reaching the foetus. (See section 4.4).

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

Breast-feeding
Like other local anaesthetics bupivacaine may enter the mother's milk, but in such small quantities that there is generally no risk of affecting neonate.

It is not known whether adrenaline enters breast milk or not, but it is unlikely to affect the breast-fed child.

Fertility
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, eg, no increased incidence of malformations.

4.7 Effects on ability to drive and use machines

Depending on dosage, local anaesthetics may have a very mild effect on mental function and may temporarily impair locomotion and co-ordination. Patients should not drive or use machinery until complete recovery from these effects has occurred.

4.8 Undesirable effects

General

The adverse reaction profile for Marcain is similar to those for other long acting local anaesthetics. 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), events caused directly (e.g. nerve trauma) or indirectly (e.g. epidural abscess) by the needle puncture. Neurological damage is a rare but well recognised consequence of regional, and particularly epidural and spinal anaesthesia.

Tabulated list of adverse reactions

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

System Organ Class	Frequency Classification	Adverse Drug Reaction
Immune system disorders	Rare	Allergic reactions, anaphylactic reaction/shock (see section 4.4)
Nervous system disorders	Common	Paraesthesia, dizziness
	Uncommon	Signs and symptoms of CNS toxicity (convulsions, paraesthesia circumoral, numbness of the tongue, hyperacusis, visual disturbances, loss of consciousness, tremor, light headedness, tinnitus, dysarthria)
	Rare	Neuropathy, peripheral nerve injury, arachnoiditis, paresis and paraplegia
Eye disorders	Rare	Diplopia
Cardiac disorders	Common	Bradycardia (see section 4.4)
	Rare	Cardiac arrest (see section 4.4), cardiac

		arrhythmias
Vascular disorders	Very Common	Hypotension (see section 4.4)
	Common	Hypertension (see section 4.5)
Respiratory, thoracic and mediastinal disorders	Rare	Respiratory depression
Gastrointestinal disorders	Very Common Common	Nausea Vomiting
Hepatobiliary disorders	Not known	Hepatic impairment/increase in AST, ALT, AlKP and bilirubin*
Renal and urinary disorders	Common	Urinary retention

* Hepatic impairment with reversible increases in AST, ALT, alkaline phosphatase and bilirubin has been observed following repeated injections or long-term infusions of bupivacaine. If signs of hepatic impairment are observed during treatment with bupivacaine, the drug should be discontinued.

4.8.1 Acute systemic toxicity

Systemic toxic reactions primarily involve the central nervous system (CNS) and the cardiovascular system. Such reactions are caused by high blood concentration of a local anaesthetic, which may appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularised areas (see also section 4.4). CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively.

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are usually light-headedness, circumoral paraesthesia, numbness of the tongue, 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. 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 drug from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the drug 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, arrhythmia 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.

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.

4.8.2 Treatment of acute toxicity

If signs of acute systemic toxicity appear, injection of the local anaesthetic should be immediately stopped and CNS symptoms (convulsion, CNS depression) must promptly be treated with appropriate airway/respiratory support and the administration of anticonvulsant drugs.

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

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.

Should cardiac arrest occur, a successful outcome may require prolonged resuscitative efforts.

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

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. (See section 4.8.1 Acute systemic toxicity and 4.8.2 Treatment of acute systemic toxicity).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC code): N01B B51

Bupivacaine is a potent amide local anaesthetic with a prolonged duration of action. It affects sensory nerves more than motor nerves and is ideal for producing analgesia without motor blockade.

5.2 Pharmacokinetic properties

In adults, the terminal half-life of bupivacaine is 3.5 hours. The maximum blood concentration varies with the site of injection and is highest after intercostal nerve blockade.

Total dose, rather than concentration, is an important determinant of peak blood levels.

Bupivacaine is biodegraded in the liver and only 6% is excreted unchanged in the urine.

In adults, adrenaline decreases peak plasma concentrations by up to 50% in brachial plexus block and by 5-25% in epidural block.

Paediatric population

In children, the pharmacokinetics are similar to that in adults.

5.3 Preclinical safety data

Bupivacaine hydrochloride and adrenaline tartrate are well established active ingredients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulphite (E223)
Sodium chloride
Hydrochloric acid /Sodium Hydroxide (for pH adjustment)
Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened: 2 years

Once opened: For single use, discard any unused solution.

6.4 Special precautions for storage

Store in a refrigerator (2^{o}C to 8^{o}C).
Do not freeze. Store in the outer carton. Protect from light.

6.5 Nature and contents of container

20 ml single dose vials of Ph. Eur. Type 1 glass (with bromobutyl rubber stopper and an aluminium cap). 5 single dose vials per carton.

6.6 Special precautions for disposal and other handling

Instructions for opening the vial

Remove cap. Gently lift ring and pull towards body in a downward direction. Completely remove aluminium seal from vial neck by rotating in an anti-clockwise motion. Position thumb directly in front of aluminium covered rubber stopper. Remove rubber stopper. Insert needle into vial and draw up solution.

For single use only. Discard any remaining solution. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1691/025/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 May 1988

Date of last renewal: 26 April 2007

10 DATE OF REVISION OF THE TEXT

July 2022