### Bupivacaine Hydrochloride

**Solution for injection**

Composition

Marcaine, solution for injection: 1 ml contains: bupivacaine hydrochloride 5.0 mg.

Marcaine adrenaline, solution for injection: 1 ml contains bupivacaine hydrochloride 5.0 mg/adrenaline 5 microg/ml.

For excipients, see List of excipients.

**Pharmaceutical form**

Solution for injection.

**Therapeutic indications**

- Surgical anaesthesia
- Acute pain management
- Acute pain management in paediatrics

**Posology and method of administration**

Adults and children above 12 years of age

The following table is a guide to dosage for the more commonly used techniques. The clinician’s experience and knowledge of the patient’s physical status are of importance in calculating the required dose. 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.

<table>
<thead>
<tr>
<th>Dosage recommendations</th>
<th>Conc. mg/ml</th>
<th>Volume ml</th>
<th>Dose mg</th>
<th>Onset min</th>
<th>Duration hours</th>
</tr>
</thead>
</table>

#### Surgical anaesthesia

<table>
<thead>
<tr>
<th>Lumbar Epidural Administration</th>
<th>Conc. mg/ml</th>
<th>Volume ml</th>
<th>Dose mg</th>
<th>Onset min</th>
<th>Duration hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>5.0</td>
<td>15-30</td>
<td>75-150</td>
<td>15-30</td>
<td>2-3</td>
</tr>
<tr>
<td></td>
<td>7.5</td>
<td>15-20</td>
<td>112.5-150</td>
<td>10-15</td>
<td>3-4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thoracic Epidural Administration</th>
<th>Conc. mg/ml</th>
<th>Volume ml</th>
<th>Dose mg</th>
<th>Onset min</th>
<th>Duration hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>2.5</td>
<td>5-15</td>
<td>12.5-37.5</td>
<td>10-15</td>
<td>1.5-2</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>5-10</td>
<td>25-50</td>
<td>10-15</td>
<td>2-3</td>
</tr>
</tbody>
</table>

#### Lumbar Epidural Administration

<table>
<thead>
<tr>
<th>Conc. mg/ml</th>
<th>Volume ml</th>
<th>Dose mg</th>
<th>Onset min</th>
<th>Duration hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>6-15</td>
<td>15-37.5</td>
<td>2-5</td>
<td>1-2</td>
</tr>
<tr>
<td>1.25</td>
<td>5-10</td>
<td>6.25-12.5</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

#### Thoracic Epidural Administration

<table>
<thead>
<tr>
<th>Conc. mg/ml</th>
<th>Volume ml</th>
<th>Dose mg</th>
<th>Onset min</th>
<th>Duration hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous infusion</td>
<td>1.25</td>
<td>5-10/h</td>
<td>6.25-12.5/h</td>
<td>-</td>
</tr>
</tbody>
</table>

#### Intra-Articular Block

<table>
<thead>
<tr>
<th>Conc. mg/ml</th>
<th>Volume ml</th>
<th>Dose mg</th>
<th>Onset min</th>
<th>Duration hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>≤ 40</td>
<td>≤ 100</td>
<td>5-10</td>
<td>2-3 after wash out</td>
</tr>
</tbody>
</table>

#### Remarks:

1) Dose includes test dose
2) 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 incidence of complications. In these circumstances, and when necessary, a group II local anaesthetic agent (e.g. chloroprocaine) may be considered.
frequency of serious adverse reactions, regardless of the local anaesthetic used, see also section 4.4.
3) In total ≤400 mg/24 h.
4) This solution is often used for epidural administration in combination with a suitable opioid for pain management. In total ≤400 mg/24 h.
5) If additional bupivacaine is used by any other techniques in the same patient, an overall dose limit of 150 mg should not be exceeded.

The doses in the table are those considered to be necessary to produce a successful block and should be regarded as a guide for use in adults. Individual variations in onset and duration occur. 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 duration may be prolonged with the adrenaline containing solutions. N.B. Risk of systemic effects of adrenaline with large volumes of adrenaline containing solutions. Unnecessarily high doses of local anaesthetics are to be avoided. In general, complete block of all nerve fibres in large nerves requires the higher concentrations of drug. In smaller nerves, or when a less intense block is required (e.g. in the relief of labour pain), the lower concentrations are 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.

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

### Paediatric patients 1 to 12 years of age

<table>
<thead>
<tr>
<th>Dosage recommendations</th>
<th>Conc. mg/ml</th>
<th>Volume ml</th>
<th>Dose mg/kg</th>
<th>Onset min</th>
<th>Duration hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pain management (per- and postoperative)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudal Epidural Administration</td>
<td>2.5</td>
<td>0.6-0.8</td>
<td>1.5-2</td>
<td>20-30</td>
<td>2-6</td>
</tr>
<tr>
<td>Lumbar Epidural Administration</td>
<td>2.5</td>
<td>0.6-0.8</td>
<td>1.5-2</td>
<td>20-30</td>
<td>2-6</td>
</tr>
<tr>
<td>Thoracic Epidural Administration</td>
<td>2.5</td>
<td>0.6-0.8</td>
<td>1.5-2</td>
<td>20-30</td>
<td>2-6</td>
</tr>
</tbody>
</table>

The doses in the table should be regarded as guidelines for use in paediatrics. Individual variations occur. In children with a high body weight a gradual reduction of the dosage is often necessary and should be based on the ideal body weight. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

In children the dosage should be calculated on a weight basis up to 2 mg/kg.

### Contraindications

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

Hypersensitivity to sodium metabisulphite in solutions containing adrenaline.

Intravenous regional anaesthesia (Bier’s block) since unintentional leakage of bupivacaine into the circulation might cause acute systemic toxic reactions.

### 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. 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. 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 intravascular injection and be appropriately trained and familiar with the diagnosis and treatment of side effects, systemic toxicity and other complications (See Overdose).

Major peripheral nerve blocks may imply the administration of a large volume of local anesthetic in areas of high vascularity, often close to large vessels where there is an increased risk of intravascular injection and/or systemic absorption which can lead to high plasma concentrations.

Patients in poor general condition due to ageing or other compromising factors such as advanced liver - or severe renal dysfunction require special attention although regional anaesthesia is frequently indicated in these patients. Patients with partial or complete heart block require special attention since Epidural anaesthesia may lead to hypotension and bradycardia. The risk of such effects can be reduced either by pre-loading the circulation or by injecting a vasopressor. Local anaesthetics may depress myocardial conduction. Patients treated with antiarrhythmic drugs class III (e.g. amiodarone) should be under close surveillance and ECG monitoring, since cardiac effects may be additive.

Hypotension should be treated promptly with e.g. ephedrine 5-10 mg intravenously and repeated as necessary. Children should be given ephedrine doses commensurate with their age and weight.

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. Certain local anaesthetic procedures such as injections in the head and neck regions may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic drug used.

Injections made inadvertently into an artery may cause immediate cerebral symptoms even at low doses.

Retrobulbar injections may very occasionally reach the cranial subarachnoid space causing temporary blindness, cardiovascular collapse, apnoea, convulsions etc. These must be diagnosed and treated promptly.

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 and other additives may aggravate tissue reactions and should be used only when indicated.

Paracervical block can sometimes cause fetal bradycardia/tachycardia, and careful monitoring of the fetal heart rate is necessary.

When bupivacaine is administered as 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 in patients with severe or untreated hypertension, poorly controlled thyrotoxicosis, ischemic heart disease, heart block, cerebrovascular insufficiency, advanced diabetes and any other pathological condition that might be aggravated by the effects of adrenaline. These solutions should also be used cautiously and in carefully restricted quantities in areas of the body supplied by end arteries, such as digits, or otherwise having a compromised blood supply. (See also Interaction)

Marcaine adrenaline solutions contain sodium metabisulphite, a sulphite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulphite sensitivity in the general population is unknown and probably low. Sulphite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.
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 mexiletin, 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.

Solutions containing adrenaline should generally be avoided or used with care in patients receiving tricyclic antidepressants since severe, prolonged hypertension may be the result. In addition, 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 penothiazines may reduce or reverse the pressor effect of adrenaline.

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

No specific interaction studies with local anaesthetics and class III anti-arrhythmic drugs (e.g. amiodarone) have been carried out, but caution is recommended.

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. 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.

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

Lactation
Like other local anaesthetics bupivacaine may enter the mother’s milk, but in such small amounts that there is generally no risk of this affecting the neonate. It is not known whether adrenaline enters breast milk or not, but it is unlikely to affect the breast-fed child.

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 co-ordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.

Undesirable effects
General
The adverse reaction profile for marcaine 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.

Table of Adverse Drug Reactions

| Very Common (>1/10) | Vascular disorders: hypotension |
| Common (>1/100 <1/10) | Gastrointestinal disorders: nausea |
| Common (>1/100 <1/10) | Nervous system disorders: paraesthesia, dizziness |
| Uncommon (>1/1,000 <1/100) | Cardiac disorders: bradycardia |
| Uncommon (>1/1,000 <1/100) | Vascular disorders: hypertension |
| Common (>1/100 <1/10) | Gastrointestinal disorders: vomiting |
| Uncommon (>1/1,000 <1/100) | Renal and urinary disorders: urinary retention |
| Rare (<1/1,000) | Nervous system disorders: Signs and symptoms of CNS toxicity (convulsions, paraesthesia circunmoral, numbness of the tongue, hyperacusis, visual disturbances, loss of consciousness, tremor, light headedness, tinnitus, dysarthria) |
| Rare (<1/1,000) | Immune system disorders: Allergic reactions, anaphylactic reaction/shock |
| Rare (<1/1,000) | Nervous system disorders: Neuropathy, peripheral nerve injury, arachnoiditis |
| Uncommon (>1/1,000 <1/100) | Eye disorders: Diplopia |
| Rare (<1/1,000) | Cardiac disorders: Cardiac arrest, cardiac arrhythmias |
| Rare (<1/1,000) | Respiratory disorders: Respiratory depression |
Overdose
Acute systemic toxicity
Systemic toxic reactions primarily involve the central nervous system (CNS) and the cardiovascular system (CVS). 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 also Special warnings and precautions for use). CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively.

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.

Central nervous system
Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are light-headedness, circumoral paresthesia, numbness of the tongue, hyperacusis, tinnitus and visual disturbances. Dysarthria, muscular twitching or tremors are more serious and precede the onset of generalized convulsions. These signs must not be mistaken for a 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 normal respiration. In severe cases apnoea may occur. Acidosis, hypocalcaemia and hypoxia increases 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
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.

In children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during general anaesthesia.

Treatment of acute toxicity
If signs of acute systemic toxicity appear injection of the local anaesthetic should be immediately stopped. If cardiovascular depression is evident (hypotension, bradycardia), ephedrine 5-10 mg i.v. should be given and repeated, if necessary, after 2-3 min. Children should be given ephedrine to commensurate with their age and weight. Should cardiac arrest occur, a successful outcome may require prolonged resuscitative efforts.

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 convulsions occur the objectives of treatment are to maintain ventilation and oxygenation, stop the convulsions and support the circulation. Oxygen must be given and ventilation assisted if necessary (mask and bag or tracheal intubation). An anticonvulsant should be given i.v. if the convulsions do not stop spontaneously in 15-20 sec. Thiopentone sodium 1-3 mg/kg i.v. will abort the convulsions rapidly. Alternatively diazepam 0.1 mg/kg bw i.v. may be used, although its action will be slow. Prolonged convulsions may jeopardise the patient’s ventilation and oxygenation. If so, injection of a muscle relaxant (e.g. succinylcholine 1 mg/kg bw) will facilitate ventilation, and oxygenation can be controlled. Early endotracheal intubation must be considered in such situations.

Pharmacodynamic properties
Pharmacotherapeutic group (ATC code): N01B B01
Bupivacaine is a long acting, amide-type local anaesthetic with both anaesthetic and analgesic
effects. At high doses it produces surgical anaesthesia, while at lower doses it produces sensory block (analgesia) with less pronounced motor block. Onset and duration of the local anaesthetic effect of bupivacaine depend on the dose and site of administration. The presence of adrenaline may prolong the duration of action for infiltration and peripheral nerve blocks but has less marked effect on epidural blocks. 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 cell membrane of the nerve fibres. The sodium channel of the nerve membrane is considered a receptor for local anaesthetic molecules. Local anaesthetics may have similar effects on other excitable membranes e.g. in the brain and myocardium. If excessive amounts of drug reach the systemic circulation, symptoms and signs of toxicity may appear, emanating from the central nervous and cardiovascular systems. Central nervous system toxicity usually precedes the cardiovascular effects as central nervous system toxicity occurs at lower plasma concentrations. Direct effects of local anaesthetics on the heart include slow conduction, negative inotropism and eventually cardiac arrest. Indirect cardiovascular effects (hypotension, bradycardia) may occur after epidural administration depending on the extent of the concomitant sympathetic block.

Preclinical safety data
Based on conventional studies with bupivacaine on safety pharmacology, single and repeated toxicity, reproduction toxicity, mutagenic potential and local toxicity, no hazards from 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:
Marcaine, solution for injection:
Sodium chloride
Sodium hydroxide/hydrochloric acid for pH adjustment to 4.0-6.0 (4.0-6.5 for 7.5 mg/ml)
Water for injections

Marcaine adrenaline, solution for injection:
Sodium chloride
Sodium metabisulphite (antioxidant)
Sodium hydroxide/hydrochloric acid for pH adjustment to 3.3 –5.0
Water for injections
Marcaine injection and Marcaine adrenaline are isotonic solutions.

Incompatibilities
The solubility of bupivacaine is limited at pH >6.5. This must be taken into consideration when alkaline solutions, i.e. carbonates, are added since precipitation might occur. In the case of adrenaline-containing solutions, mixing with alkaline solutions may cause rapid degradation of adrenaline.

Shelf-life
Please see outer carton

Special precautions for storage
Marcaine without adrenaline: Do not store above 25°C. Do not freeze.
Marcaine with adrenaline: Do not store above 15°C. Do not freeze. Protect from light.

Pack size
Please see outer carton

Instructions for use/handling
The solutions are free from preservative and intended for single use only. Any remaining solution must be discarded.
Re-sterilisation of Marcaine is not recommended. Due to the instability of adrenaline, products containing adrenaline must not be re-sterilized. Adequate precautions should be taken to avoid prolonged contact between local anaesthetic solutions containing adrenaline (low pH) and metal surfaces (e.g. needles or metal parts of syringes), since dissolved metal ions, particularly copper ions, may cause severe local irritation (swelling, oedema) at the site of injection and accelerate the degradation of adrenaline.

Date of revision of the text
March 2005