

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bupivacaine Hydrochloride 5 mg/ml (0.5% w/v) Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Bupivacaine Hydrochloride 5 mg/ml (0.5% w/v) Solution for Injection contains 5 mg bupivacaine hydrochloride per ml (as monohydrate).

Each 5ml ampoule contains 25 mg bupivacaine hydrochloride.

Each 10ml ampoule contains 50 mg bupivacaine hydrochloride.

Each 20ml ampoule contains 100 mg bupivacaine hydrochloride.

For excipients see 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

Clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Local Infiltration.
- Peripheral Nerve Blocks.
- Central Nerve Blocks (Epidural and Spinal Anaesthesia).

For local or regional anaesthesia and/or analgesia for surgical, diagnostic and obstetric procedures.

4.2 Posology and method of administration

ADULTS:

The following recommended bupivacaine doses (Table 1) serve as a guideline for an average adult with a body weight of approximately 70 kg.

The dosage varies and depends upon the area(s) to be anaesthetised, the vascularity of the tissues, the number of neuronal segments to be blocked, individual tolerance and the anaesthetic technique that is to be used.

The lowest dosage needed to provide effective anaesthesia and / or analgesia should always be administered.

The maximum dosage must always be determined by evaluating the size and physical status of the patient, and by considering the usual rate of systemic absorption from a particular injection site. Based on body weight, the maximum recommended dose of bupivacaine hydrochloride is 2 mg/kg, and up to a maximum of 150 mg within a 4-hour period. The maximum recommended adult dose during a 24-hour period is 400 mg.

CHILDREN:

Bupivacaine hydrochloride may be also used to provide anaesthesia and / or analgesia in children. As with other local anaesthetics, use of bupivacaine for paediatric anaesthesia requires a careful assessment of the risk/benefit ratio by the

anaesthetist administering the dose. Dosage requirements vary and depend upon the areas to be anaesthetised, the vascularity of the tissues, the number of neuronal segments to be blocked, individual tolerance, the intended anaesthetic technique and (for paediatric patients) the physiological maturity of the patient. The lowest dosage needed to provide effective anaesthesia and / or analgesia should always be administered.

Because the number of possible variables affecting dosing in children is considerable, specific guidance is not provided in Table 1. Reduced doses should always be used, and the exact requirements for each patient should be established by an experienced anaesthetist with reference to current professional practice guidelines and recognised standard texts.¹

The maximum recommended dose of bupivacaine hydrochloride in children, based upon body weight is 2 mg/kg. For epidural infusion, after a loading dose of 0.25 - 0.75 mg/Kg the maximum rate of administration in children 6 months or younger is 0.2 mg/kg/hour and in children older than 6 months is 0.4 mg/kg/hour. The maximum recommended dose during a 4-hour period is 1 mg/kg for children 6 months or younger and 2 mg/kg for children older than 6 months. Total dose during a 24-hour period has not been established, recommended maximum dose should not exceed 6 mg/Kg. The use of bupivacaine over 48 hours is not recommended in children 6 months of age or younger. Infusion rates should be reduced in patients with risk factors for seizures.

¹ Miller RD, “Anesthesia”, Churchill Livingston, 5th Edition, 1999, ISBN: 0443079889, and Dalens BJ, “Regional anaesthesia in infants, children and adolescents”, Waverley, 1995, ISBN: 0683096523.

ELDERLY PATIENTS:

Elderly or debilitated patients might be more sensitive to the standard dosage, with an increased risk and severity of toxic reactions of the central nervous and cardiovascular system. Dose reduction should be considered, but must take into account the fact that this may lead to insufficient anaesthesia.

TABLE 1: RECOMMENDED DOSING FOR BUPIVACAINE IN COMMON TYPES OF ANAESTHESIA (FOR AN AVERAGE 70KG ADULT)					
Type of Blockade	Concentration		Dose Range (minimum-maximum)		
	mg/ml	% w/v	ml	mg	mg/Kg
LOCAL INFILTRATION	2.5	0.25	Up to 60	Up to 150	Up to 2
	5	0.5	Up to 30	Up to 150	Up to 2
PERIPHERAL NERVE BLOCKS					
○ Diagnostic or therapeutic blocks	2.5	0.25	1-40	2.5-100	0.04-1.4
○ Digital blocks	2.5	0.25	1-5	2.5-12.5	0.04-0.18
○ Intercostal blocks (per nerve, up to a total of 10 nerves)	5	0.5	2-3	10-15	0.14-0.21
○ Major nerve blocks (e.g. brachial plexus)	5	0.5	15-30	75-150	1.1-2

CENTRAL NERVE BLOCKS					
Thoracal Epidural					
○ Surgical procedures	5	0.5	5-10	25-50	0.36-0.71
○ Post-operative pain relief	2.5	0.25	5-15	12.5-37.5	0.18-0.54
Note: The dose includes the test dose.					
Thoracal Epidural – continuous infusion					
○ Post-operative pain relief (thoracal and upper abdominal surgery)	2.5	0.25	4-7.5 per hour	10-18.75 per hour	0.14-0.27
Note: Initial bolus dose of 2.5 or 5 mg/ml is needed to obtain analgesia. Total up to 400 mg in 24 hours.					
Lumbar Epidural					
○ Surgical procedures (including Caesarean section)	5	0.5	15-30	75-150	1.1-2
○ Pain relief during labour	2.5	0.25	6-15	15-37.5	0.21-0.54
Note: The dose includes the test dose.					
Lumbar Epidural – continuous infusion					
○ Post-operative pain relief and pain relief during labour	2.5	0.25	5-7.5 per hour	12.5-18.75 per hour	0.18-0.27
Note: Initial bolus dose of 2.5 or 5 mg/ml is needed to obtain analgesia. Total up to 400 mg in 24 hours.					
Caudal Epidural					
○ Surgical procedures	5	0.5	20-30	100-150	1.43-2
○ Pain relief during labour	2.5	0.25	6-12	15-30	0.21-0.43
Spinal	5	0.5	2-4	10-20	0.14-0.28

At a concentration of 5 mg/ml bupivacaine has a duration of action of 2 – 5 hours after a single epidural injection and of more than 12 hours after a peripheral nerve block. The onset of anaesthesia is slower than with lidocaine, especially when used for major nerve blocks, but is generally between 15 and 30 minutes for major nerve blocks and typically between 2 to 10 minutes for spinal nerve block. When used at a lower concentration (2.5 mg/ml) the motor blocking effect will be less and the duration of action shorter.

Bupivacaine is an isobaric solution, with baricity similar to that of cerebrospinal fluid (CSF). The spread of anaesthesia depends on several factors including the volume of solution and the position of the patient during and following the injection. It should be understood that the level of spinal anaesthesia achieved with any local anaesthetic could be

unpredictable in a given patient.

Due to increased risk of unintentional high spinal blockade, the dose should be reduced in the elderly and in women in late stages of pregnancy. The effects of administering bupivacaine 0.5% at doses of greater than 4 ml have not been studied; hence dosages greater than 4 ml are not recommended.

It is recommended that bupivacaine should be warmed to room temperature prior to use, because injection of a cold solution may be painful.

4.3 Contraindications

- Known hypersensitivity to bupivacaine hydrochloride, anaesthetics of the amide type or any of the excipients.
- Bupivacaine hydrochloride must not be used for intravenous regional anaesthesia (Bier's Block), because accidental leakage of bupivacaine through the tourniquet can cause systemic toxic reactions.
- Bupivacaine hydrochloride must not be administered to inflamed or infected application sites.
- Bupivacaine hydrochloride must not be used for central nerve block (spinal and epidural) if active disease of the central nervous system is present, such as: meningitis, poliomyelitis, intracranial haemorrhage, sub-acute combined degeneration of the spinal cord due to pernicious anaemia, cerebral and spinal tumours, tuberculosis of the spine, in the case of cardiogenic or hypovolaemic shock, or in the presence of significant coagulopathy or anticoagulation therapy, and in obstetrics with threatening or existing haemorrhage.
- Bupivacaine hydrochloride must not be used for obstetric paracervical block.

4.4 Special warnings and precautions for use

With the exception of the simplest procedures, all forms of local and regional anaesthesia should be performed in well-equipped facilities and administered by staff trained and experienced in the required anaesthetic techniques, and able to diagnose and treat any unwanted adverse effects that may occur.

Adequate medical provision for resuscitation (such as instruments for clearing the airways, resuscitation equipment) and management of adverse reactions should be available for immediate use. Whenever larger blockades are required an intravenous cannula should be inserted before the local anaesthetic is injected.

Extreme caution should be exercised to avoid inadvertent intravascular injections. Careful aspiration is recommended before and during injection. In epidural anaesthesia, a test dose of 3 to 5 ml bupivacaine hydrochloride is recommended, preferably with adrenaline. Intravascular injection of adrenaline can be readily identified by an increase in heart frequency. Continuous communication with the patient is recommended, as well as monitoring of the heart rate after administration of the test dose. Re-aspirate before administration of the complete dose. The complete dose should be slowly injected by gradually increasing the dose and by continuously communicating with the patient. If any toxic symptoms occur the administration should be immediately stopped.

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.

Epidural or spinal anaesthesia with any local anaesthetic 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 an intravenous vasopressor and / or fluids.

Particular care should be taken in the case of certain types of anaesthesia, as follows:

Type of Anaesthesia	Particular Precautions to Note
Head and neck	Caution is required to avoid unintentional intravascular injection, which can result in cerebral toxicity, even at low doses.
Retrobulbar Injection	In rare cases the local anaesthetic may leak into the subarachnoid space resulting in local anaesthetic toxic reactions such as temporary blindness, cardiovascular collapse, apnoea convulsions etc. These complications must be recognised and treated immediately.
Retrobulbar and peribulbar injection	With this type of injection there is a small risk of persistent eye muscle dysfunction arising from damage and/or local toxic effects on the muscles and/or nerves. The severity of dysfunction depends upon the degree of damage caused, the concentration of the local anaesthetic applied and the duration of tissue exposure.
Central blocks	The possibility of serious hypotension and bradycardia must be taken into account, particularly in hypovolaemic patients. Caution is required in patients with reduced cardiovascular reserves because they are possibly less able to compensate for the reduced atrioventricular conduction caused by bupivacaine.

In order to minimize the risk of dangerous side effects special attention is also required in the following patient groups:

- Elderly patients and patients with poor general health: acidosis or hypoxia in the patient increases the risk and severity of toxic reactions of the central nervous system or the cardiovascular system.
- Patients with serious liver and/or kidney insufficiency.
- Patients with a partial or total AV block: Local anaesthetics can cause a slowing down of conduction.
- Patients under treatment with beta-blockers.
- Patients with coagulation disorders or ongoing anticoagulation treatment.

If a central nerve block is intended concomitant therapy with NSAIDs (inclusive acetylsalicylic acid) must be taken into account or be stopped at an appropriate time beforehand.

In obstetrics a possible complication after administration of Bupivacaine is arterial hypotension.

The possibility of cross-hypersensitivity to other amide-type local anaesthetics must be taken into account.

In rare cases cardiac arrest has been reported without prior central nervous system symptoms. This was probably due to overdose caused by unintentional intravascular injection (see Section 4.9: “Overdose”).

There is a risk of additive toxic effects if bupivacaine is administered at the same time as antiarrhythmic drugs such as tocainide and volatile anaesthetics.

4.5 Interaction with other medicinal products and other forms of interaction

Bupivacaine should be used with care in patients receiving anti-arrhythmic drugs with local anaesthetic activity, such as lidocaine and aprindin, since their toxic effects may be additive.

See also Sections 4.3 and 4.4.

4.6 Pregnancy and lactation

There is no evidence of untoward effects in human pregnancy. Studies in animals have shown reproductive toxicity (see section 5.3). The human risk is unknown. Bupivacaine should not therefore be given in early pregnancy unless the benefits are considered to outweigh the risks.

As with other local anaesthetics used for local and regional anaesthesia during pregnancy, bupivacaine passes through the placenta.

Although the total bupivacaine concentrations in the umbilical cord blood are lower than the mother's serum concentrations, the free bupivacaine concentration is the same. Foetal bradycardia may occur following paracervical block.

Bupivacaine is secreted into breast milk. However, the concentrations are so low that at therapeutic doses no harmful effects on the neonate are anticipated.

4.7 Effects on ability to drive and use machines

In therapeutic doses local anaesthetics have no effect on mental functions. However, they can affect the motor system in parts of the body influenced by the local anaesthetic block. The doctor should always assess the potential effects on the patient and advise the patient accordingly.

4.8 Undesirable effects

General

Undesirable effects resulting from overdose or unintentional intravascular injection are very significant and can be serious (see Section 4.9: "Overdose").

Bupivacaine is more likely to produce acute cardiac toxicity than other local anaesthetics. Cardiovascular reactions are related to depression of the conduction system of the heart and myocardium leading to decreased cardiac output, heart block, hypotension, bradycardia, and sometimes ventricular arrhythmias, including ventricular tachycardia, ventricular fibrillation and cardiac arrest. Usually these will be preceded or accompanied by major CNS toxicity, such as convulsions, but in rare cases cardiac arrest has occurred without preceding CNS effects. Hypoxia and acidosis modify the pharmacokinetics and pharmacodynamics of local anaesthetics and may increase the risk of anaesthetic toxicity.

Hypersensitivity reactions

Hypersensitivity reactions to local amide type anaesthetics rarely occur.

Neurological complications

Neurological reactions to local amide type anaesthetics are very rare. In most cases these reactions are a function of the total administered dose of the local anaesthetic, the manner in which the anaesthetic has been administered and the physical condition of the patient. Many of these effects may be related to the techniques used, with or without the contribution of the medication being used. Neurological reactions as a result of regional anaesthesia are persistent anaesthesia, paraesthesia, paresis or plegia of the lower extremities and loss of sphincter control.

Acute systemic toxicity

Serious reactions caused by bupivacaine are identical to those observed with other local anaesthetics and typically occur as a result of high systemic concentrations, as in the case of overdose, too rapid absorption and through unintentional intravascular injection (see Section 4.9: "Overdose").

Frequency table:

Frequency	System	Symptoms
Common (>1/100 - <1/10)	CNS	Headache (related to the anaesthetic technique)
	Circulatory	Fall in blood pressure and bradycardia (primarily with epidural anaesthesia)
Rare (>1/10,000 - <1/1,000)	General	Allergic reactions, in the most serious cases – anaphylactic shock.
	Circulatory	Myocardial depression and cardiac arrest (with absolute or relative overdosage)
	CNS	Unconsciousness and seizures (with absolute or relative overdosage)

4.9 Overdose

Acute systemic toxicity

Acute systemic toxicity arising from accidental intravascular injections occurs rapidly (within one to three minutes).

With overdosing, acute toxicity occurs over a longer period, as the peak plasma concentration rises; toxic effects typically occur up to 20-30 minutes after administration and relate to the effect of bupivacaine on the central nervous and cardiovascular systems.

Effects on the Central Nervous System (CNS):
In overdosing, the toxic effects of bupivacaine on the CNS occur gradually and in increasing seriousness.

They include:

- Initially: Circumoral paraesthesia, numbness of the tongue, dizziness, hyperacusis, and tinnitus.
- Visual disturbance and muscle tremor: These are more serious and must not be mistaken for nervous behaviour because they may precede the occurrence of general seizure.
- Loss of consciousness and grand mal seizures lasting from a few seconds to several minutes.
- Hypoxia and hypercapnia occurring shortly after seizures, resulting from increased muscle activity, together with disturbances of normal respiration. In more serious cases, apnoea may occur.
- Acidosis, which results in exacerbation of the toxic effects.

The rate of recovery from the toxic effects of bupivacaine overdose is related to the rate of which the blood concentration falls. Where a small dose has been given, recovery can occur quite quickly.

Effects on the Cardiovascular System:
In cases of serious overdosing, cardiovascular effects are seen; including hypotension, bradycardia, arrhythmias and (at high concentrations) cardiovascular collapse.

Generally, CNS symptoms are seen before adverse cardiovascular effects arise, providing that the patient is not fully anaesthetized or heavily sedated with drugs such as benzodiazepines or barbiturates.

Treatment of acute toxicity

If signs of acute systemic toxicity are suspected, administration of bupivacaine must be stopped immediately.

Because seizures may occur appropriate drugs and equipment should always be readily available.

The principal aims of treatment are:

- To maintain oxygenation.
- To stabilise the circulatory system.
- To control the seizures.

Oxygen should be immediately administered; if necessary by bag and mask (assisted) ventilation.

If seizures do not resolve spontaneously within 15 – 20 seconds, an anticonvulsant drug, such as thiopental (100 to 150 mg) should be administered intravenously. Benzodiazepines (for example, Diazepam (5-10 mg i.v.)) may also be administered. Succinylcholine may also be used to quickly treat muscle cramps, but administration of this drug requires tracheal intubation and artificial ventilation, and must therefore only be administered by experienced medical staff, familiar with this technique.

If signs of cardiovascular depression are evident (such as hypotension and bradycardia), ephedrine (5 – 10 mg) should be administered intravenously, and a second dose provided, if necessary, after two to three minutes.

If circulatory arrest occurs, cardiopulmonary resuscitation should be immediately initiated: Adrenaline (0.1-0.2 mg) should be immediately administered intravenously or intracardially and if necessary repeated. Optimal oxygenation, ventilation, circulatory maintenance and treatment of acidosis must also be provided, because hypoxia and acidosis can exacerbate the acute toxic effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Local Anaesthetic. ATC Code: N01BB01.

Bupivacaine is a **local** amide type **anaesthetic** with a **long-term effectiveness** and a high anaesthetic activity.

The mechanism of action is based on reduced sodium ion permeability of the nerve cell membrane. As a result of this, the depolarisation rate is reduced and the excitation threshold is increased, which leads to a reversible loss of feeling.

At a concentration of 5 mg/ml bupivacaine has a duration of action of 2 – 5 hours after a single epidural injection and of more than 12 hours after a peripheral nerve block. The onset of anaesthesia is slower than with lidocaine, especially when used for major nerve blocks, but is generally between 15 and 30 minutes for major nerve blocks and typically 2 to 10 minutes for spinal nerve block. When used at a lower concentration (2.5 mg/ml) the motor blocking effect will be less and the duration of action shorter.

It should be noted that the individual variations in motor block responses to bupivacaine are large.

5.2 Pharmacokinetic properties

Absorption and distribution

The extent of systemic absorption of bupivacaine depends upon the dose, the manner of administration and the extent of vascularisation of the site of injection. Increased levels of alpha acid glycoproteins, as can occur after major surgery, can give rise to an increase in the total bupivacaine plasma concentrations. However, the free bupivacaine concentration remains the same and this explains why total bupivacaine concentrations higher than the limit of 2.6 to 3 mg/l (which is considered toxic) are usually well tolerated by patients.

Metabolism and excretion

Bupivacaine is largely metabolised in the liver and eliminated through the kidneys. As with other local amide type anaesthetics, elimination mainly occurs through biotransformation. Only 6% is eliminated unchanged.

5.3 Preclinical safety data

At supratherapeutic doses there is evidence of decreased pup survival in rats and embryological effects in rabbits if bupivacaine is administered during pregnancy. Further preclinical data are of no more relevance to the prescriber than that stated in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Sodium chloride
Sodium hydroxide
Water for injections

6.2 Incompatibilities

The addition of bupivacaine to alkaline solutions causes precipitation of bupivacaine because the solubility of bupivacaine is limited at pH levels greater than 6.5.

The solutions should not come in contact with metals, for example needles, or with parts of the syringe for a long period of time, since metal ions in the solution may lead to swelling at the injection site.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

5 ml, 10 ml, or 20 ml Type 1 colourless glass ampoules, each of which is supplied in packs of 10 ampoules.

Not all presentations may be marketed.

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

Each ampoule is intended for **single use** only.

The solution should be immediately used after opening the ampoule.

Any unused product should be disposed of after first use in accordance with local requirements.

Only use bupivacaine if the solution in the ampoule is completely clear and the ampoule is undamaged.

7 MARKETING AUTHORISATION HOLDER

Baxter Healthcare Ltd.
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8 MARKETING AUTHORISATION NUMBER

PA 167/112/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 May 2003

10 DATE OF REVISION OF THE TEXT