pharmaniaga®

Bupicaine D 0.5% w/v Solution for Injection

COMPOSITION:
Each 4mL ampoule contains Bupivacaine hydrochloride 20.00mg, Dextrose anhydrous 290.92mg, Hydrochloric acid q.s. and Sodium hydroxide q.s.

PRODUCT DESCRIPTION:
A clear, colourless solution.

PHARMACODYNAMICS
Bupicaine D contains bupivacaine, which is a long-acting local anaesthetic of the amide type. Bupivacaine reversibly blocks impulse conduction in the nerves by inhibiting the transport of sodium ions through the nerve membrane. Similar effects can also be seen on excitatory membranes in the brain and myocardium.

Bupicaine D is intended for hyperbaric spinal anaesthesia. The relative density of the solution for injection is 1.026 at 20°C (equivalent to 1.021 at 37°C) and the initial distribution into the subarachnoid space is markedly influenced by gravity. For administration into the spine, a small dose is given, which gives a relatively low concentration and short duration of effect.

PHARMACOKINETICS:
Bupivacaine is very liposoluble with an oil/water distribution coefficient of 27.5. Bupivacaine displays complete and bi-phasic absorption from the subarachnoid space, with half-lives for the two phases of approx. 50 and approx. 400 minutes, with large variations. The slow absorption phase is the rate-determining factor in the elimination of bupivacaine, which explains why the apparent half-life is longer than after intravenous administration.

Absorption from the subarachnoid space relatively slow, which, in combination with the low dose required for spinal anaesthesia, gives a relatively low plasma concentration (approx. 0.4 mg/ml per 100 mg injected) After intravenous administration, total plasma clearance is approx. 0.58 l/min, the volume of distribution in steady state is approx. 73 l, the elimination half-life is 2.7 hours, and the hepatic extraction ratio is approx. 0.40.

Bupivacaine is metabolised almost completely in the liver, predominantly through aromatic hydroxylation to 4-hydroxybupivacaine and N-dealkylation to PPX, both of which are mediated by cytochrome P450 3A4. Clearance is thus dependant on hepatic perfusion and the activity of the metabolising enzyme. Bupivacaine crosses the placenta and the concentration of free bupivacaine is the same in the mother and the foetus. However, the total plasma concentration is lower in the foetus, which has a lower degree of protein binding.

INDICATIONS:
Spinal anaesthesia for surgery, e.g. urological surgery and surgery on the lower limbs lasting 2-3 hours, abdominal surgery lasting 45-60 minutes.

RECOMMENDED DOSAGE:
Bupicaine D should only be used by clinicians with experience of regional anaesthesia or under their supervision. The lowest possible dose for adequate anaesthesia should be used.

The doses given below are guides for adults and the dosage should be adjusted to the individual patient.

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

Indication	Dose (ml)	Dose (mg)	Time to onset of effect in minutes (approx.)	Duration of effect in hours (approx.)
Urological surgery	1.5-3 ml	7.5-15 mg	5-8 min	2-3 hours
Surgery on lower limbs, including hip surgery	2-4 ml	10-20 mg	5-8 min	2-3 hours
Abdominal surgery (including caesarean section)	2-4 ml	10-20 mg	5-8 min	45-60 min

The recommended site of injection is below L3-L4 intervertebral space. There is currently no experience of doses higher than 20 mg.

A spinal injection is given only after the subarachnoid space has been clearly identified by means of lumbar puncture (clear cerebrospinal fluid runs out via the spinal needle or is seen on aspiration). In the event of unsuccessful anaesthesia, a new attempt to administer the drug should only be made by injecting at a different level and with a smaller volume. One cause of lack of effect may be poor intrathecal distribution of the drug, and this can be helped by altering the patient's position.

ROUTE OF ADMINISTRATION:
Parenteral (Intrathecal Injection)

CONTRAINDICATIONS:
Hypersensitivity to the active substance or to any of the excipients. Hypersensitivity to local anaesthetics of the amide type.
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.
- Spinal stenosis and active disease (e.g. spondylitis, tuberculosis, tumour) 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.

WARNING AND PRECAUTION:
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 IV 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 section Side Effect and Overdose.

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. Should cardiac arrest occur, a successful outcome may require prolonged resuscitative efforts. High systemic concentrations are not expected with doses normally used for intrathecal anaesthesia.

There is an increased risk of high or total spinal blockade, resulting in cardiovascular and respiratory depression, in the elderly and in patients in the late stages of pregnancy. The dose should therefore be reduced in these patients. Intrathecal anaesthesia with any local anaesthetic can cause hypotension and bradycardia which should be anticipated and appropriate precautions taken. These may include preloading the circulation with crystalloid or colloid solution. If hypotension develops it should be treated with a vasopressor such as ephedrine 10–15 mg intravenously. 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. Neurological injury is a rare consequence of intrathecal anaesthesia and may result in paraesthesia, anaesthesia, motor weakness and paralysis. Occasionally these are permanent.

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 Interaction with Other Medication)

INTERACTIONS WITH OTHER MEDICAMENTS:
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 Warning and Precaution).

Incompatibilities
Additional to Spinal solutions are not recommended.

PREGNANCY AND LACTATION:
Pregnancy
There is no evidence of untoward effects in human pregnancy. Bupicaine D should not therefore be given in early pregnancy unless the benefits are considered to outweigh the risks. (See also section Warnings and Precautions).
It should be noted that the dose should be reduced in patients in the late stages of pregnancy.

Lactation
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.

SIDE EFFECTS/ADVERSE REACTIONS:
The adverse reaction profile for Bupicaine D is similar to those for other long acting local anaesthetics used for intrathecal anaesthesia. Frequencies are defined as very common, common, uncommon, rare, very rare or not known (cannot be estimated from the available data).

Table of Adverse Drug Reactions

System Organ Class	Frequency Classification	Adverse Drug Reaction
Immune system disorders	Rare	Allergic reactions, anaphylactic shock
Nervous system disorders	Common	Postdural puncture headache
	Uncommon	Paraesthesia, paresis, dysaesthesia
	Rare	Paralysis, neuropathy, arachnoiditis Total unintentional spinal block, paraplegia
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

Adverse reactions caused by the drug 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 abcess) by needle puncture or events associated to cerebrospinal leakage (e.g. postdural puncture headache).

Acute systemic toxicity
Bupicaine D, 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.

Treatment of acute systemic toxicity
No treatment is required for milder symptoms of systemic toxicity but if convulsions occur then it is important to ensure adequate oxygenation and to arrest the convulsions if they last more than 15–30 seconds. Oxygen should be given by face mask and the respiration assisted or controlled if necessary. Convulsions can be arrested by injection of thiopental 100–150 mg intravenously or with diazepam 5–10 mg intravenously. Alternatively, succinylcholine 50–100 mg intravenously may be given but only if the clinician has the ability to perform endotracheal intubation and to manage a totally paralysed patient.

High or total spinal blockade causing respiratory paralysis should be treated by ensuring and maintaining a patent airway and giving oxygen by assisted or controlled ventilation. Hypotension should be treated by the use of vasopressors, e.g. ephedrine 10–15 mg intravenously and repeated until the desired level of arterial pressure is reached. Intravenous fluids, both electrolytes and colloids, given rapidly can also reverse hypotension.

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.

SYMPTOMS AND TREATMENT OF OVERDOSE:
Bupicaine D 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 Side Effects under subheading Acute Systemic Toxicity & Treatment of Acute Systemic Toxicity).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE:
Bupicaine D has minor influence on the 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.

INSTRUCTION FOR USE:
Instructions for use, handling and disposal
The solution should be used immediately after opening of the ampoule. Any remaining solution should be discarded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

STORAGE CONDITION:
Store below 30°C. Do not freeze.
Retain in carton till time of use.

SHELF LIFE:
36 months from date of manufacture.

DOSAGE FORMS AND PACKING AVAILABLE:
Bupicaine D 0.5% w/v Solution for Injection:
Sterile individual packing ampoule
(Sterile Pack)
5 x 4mL ampoule (clear ampoule of glass Type 1)

PRODUCT REGISTRATION HOLDER/MANUFACTURER:
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