0500401/3

BUPIVACAINE HYDROCHLORIDE

SENSORCAINE 0.5% Heavy
5 mg/mL Solution for Spinal Injection
Local Anesthetic

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1. FORMULATION
1 mL solution for injection contains: Bupivacaine hydrochloride 5 mg

2. PHARMACEUTICAL FORM
Solution for injection.

3. CLINICAL PARTICULARS
3.1 Therapeutic 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.

3.2 Dosage and method of administration
Bupivacaine hydrochloride (SENSORCAINE) Spinal Heavy 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 elderly patients and patients in 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 injection site is the 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.

3.3 Contraindications
Hypersensitivity to local anaesthetics of the amide type or to other components of the product. Diseases of the central nervous system (e.g. meningitis, poliomyelitis, intracranial haemorrhage). Local pyogenic infection at or adjacent to the injection site. Spinal stenosis and active disease (e.g. spondylitis, tumour) or trauma (e.g. fracture of the spine). Septicaemia. pernicious anaemia with subacute degeneration of the spinal cord. Spinal anaesthesia should not be given to patients in shock. Nor should spinal anaesthesia be given to patients with coagulation disorders or to patients receiving ongoing anticoagulation treatment.

3.4 Special warning and precautions for use
One should be aware that spinal anaesthesia can sometimes lead to major blocks, with paralysis of intercostal muscles and the diaphragm, especially in pregnant women.

Caution should be exercised in patients with degree II or III AV block since local anaesthetics can lower the conduction capacity of the myocardium. Elderly patients and patients with severe hepatic disease, severely impaired renal function or in generally reduced general condition also require special attention.

Patients treated with class III anti-arrhythmic drugs (e.g. amiodarone) should be closely observed and ECG monitoring should be considered, since the cardiac effects of bupivacaine and class III anti-arrhythmic drugs can be additive.

Like all local anaesthetic drugs, bupivacaine can cause acute central nervous and cardiovascular toxic effects in cases of use leading to high concentrations in the blood. This applies particularly after inadvertent intravascular administration.

Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported in association with high systemic concentrations of bupivacaine. However, with the doses normally used for spinal anaesthesia high systemic concentrations are uncommon.
An uncommon, but dangerous, side effect in spinal anaesthesia is extensive or total spinal blockade, which results in cardiovascular depression and respiratory depression. The cardiovascular depression is caused by extensive sympathetic blockade, which can result in hypotension and bradycardia, or even cardiac arrest. Respiratory depression can be caused by blockade of the innervation of the respiratory muscles, including the diaphragm. There is an increased risk of extensive or total spinal blockade in elderly patients and patients in late stages of pregnancy. The dose should therefore be reduced for these patients.

Intrathecal 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.

In rare cases spinal anaesthesia can cause neurological damage, resulting in paraesthesia, anaesthesia, motor weakness and paralysis. Neurological disorders, such as multiple sclerosis, hemiplegia, paraplegia and neuromuscular disturbances are not thought to be adversely affected by spinal anaesthesia, but caution should be exercised.

3.5 Interactions with other medicinal products and other forms of interactions
Bupivacaine should be used with caution with other local anaesthetics or drugs that are structurally similar to local anaesthetics, i.e. class IB anti-arrhythmic drugs, as the toxic effects are additive.
No specific interaction studies with local anaesthetics and class III anti-arrhythmic drugs (e.g. amiodarone) have been carried out, but caution is recommended (See section 3.4 Special warning and special precautions for use).

3.6 Pregnancy and Lactation
Pregnancy
No known risks for the foetus from use during pregnancy. However, note that the dose should be reduced for patients in late stages of pregnancy. (See section 3.4 Special warnings and special precautions for use).

Lactation
Bupivacaine passes into breast milk, but the risk of this affecting the child appears unlikely with therapeutic doses.

3.7 Effects on ability to drive and use machines
Depending on the dose and method of administration, bupivacaine can have a transient effect on movement and coordination.

3.8 Undesirable effects

Undesirable effects caused by the product itself can be difficult to distinguish from the physiological effects of the nerve block (e.g. fall in blood pressure, bradycardia, temporary urinary retention), events caused directly by the needle puncture (e.g. spinal haematoma) or caused indirectly by the needle puncture (e.g. meningitis, epidural abscess) or events associated with leakage of cerebrospinal fluid (e.g. post lumbar puncture headache).	
Very common (>1/10)	*General:* Nausea *Circ.:* Hypotension, bradycardia
Common (>1/100)	*CNS:* Post lumbar puncture headache *GI:* Vomiting *Genitourinary:* Urinary retention, urinary incontinence
Uncommon (1/100-1/1000)	*CNS:* Paraesthesia, paresia, dysaesthesia *Musculoskel.:* Muscle weakness, back pain
Rare <1/1000)	*Circ.:* Cardiac arrest *General:* Allergic reactions, anaphylactic shock *CNS:* Accidental total spinal blockade, paraplegia, paralysis, neuropathy, arachnoiditis *Airways:* Respiratory depression

3.9 Overdose

Bupivacaine can cause acute toxic effects of a central nervous and cardiovascular nature if it is given in high doses, especially if it is administered intravascularly. However, the dose used in spinal anaesthesia is low (≤ 20 % of the dose used for epidural anaesthesia) and thus the risk of overdosage is unlikely. In cases of concomitant administration with other local anaesthetics, however, systemic toxic effects may occur, as the toxic effects are additive.

Treatment of complications
In cases of total spinal blockade adequate ventilation must be ensured (patent airways, oxygen, intubation and controlled ventilation if necessary). If there is a fall in blood pressure a vasopressor (preferably with an inotropic effect) should be given, e.g. ephedrine 5-10 mg intravenously.
If signs of acute systemic toxicity occur the administration of local anaesthetics must be stopped immediately. Treatment must be given to maintain good ventilation, oxygenation and circulation. Oxygen must always be given, and assisted ventilation if necessary. If convulsions do not cease spontaneously within 15-20 seconds, thiopentone sodium 1-3 mg/kg should be given intravenously to facilitate ventilation or diazepam 0.1 mg/kg intravenously (acts rather more slowly). Prolonged seizures jeopardise the patient's respiration and oxygenation. Injection of muscle relaxants (e.g. suxamethonium 1 mg/kg) creates more favourable conditions for ventilation and oxygenation of the patient, but requires experience of tracheal intubation and controlled ventilation. In cases of a fall in blood pressure/ bradycardia, a vasopressor should be given (e.g. ephedrine 5-10 mg intravenously, which may be repeated after 2-3 minutes). In the event of circulatory arrest, cardiopulmonary resuscitation should be instituted immediately. It is important to maintain good oxygenation, respiration and circulation, and to treat acidosis.

Children must be given doses in proportion to their age and bodyweight for treatment of systemic toxicity.

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamic properties

Pharmacotherapeutic group: Local anaesthetics
ATC code: N01B B01.

Bupivacaine hydrochloride (SENSORCAINE) Spinal Heavy 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.

Bupivacaine hydrochloride(SENSORCAINE) Spinal Heavy 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. Bupivacaine hydrochloride(SENSORCAINE) Spinal (without glucose) produces a less predictable block, but with a longer duration of effect than Bupivacaine hydrochloride (SENSORCAINE) Spinal Heavy (with glucose).

4.2 Pharmacokinetic Properties

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 is 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 dependent 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.

5. PHARMACEUTICAL PARTICULARS

5.1 Incompatibilities

Additions to spinal solutions are not recommended.

5.2 Shelf Life

Please refer to outer carton.
The solution must be used as soon as possible after the container has been opened.

5.3 Storage

Store at a temperature not exceeding above 25°C. Do not freeze.

5.4 Availability

Bupivacaine hydrochloride (SENSORCAINE) - Box of 5 x 4 mL ampoule
DR-XY2442

Date of Renewal of Authorization 24 Mar 2020

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA at www.fda.gov.ph and to Aspen Philippines at PV.Phils@PH.AspenAP.com
The patient should seek medical attention immediately at first sign of any adverse drug reaction.

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