Marcaine Spinal 0.5%

1 NAME OF THE MEDICINAL PRODUCT

Marcaine Spinal 0.5%

Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains: bupivacaine hydrochloride 5 mg

Excipient(s) with known effect: Sodium 3.1 mg/ml

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Spinal anaesthesia for surgery.

4.2 Posology and method of administration

Marcaine Spinal should only be used by clinicians with experience in 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.)
Surgery on lower limbs, including hip surgery	2-4 ml	10-20 mg	5-8 min	1.5-4 hours

The recommended injection site is the L_3-L_4 intervertebral space.
There is currently no experience with doses higher than 20 mg. An intravenous input port should be created before administration of Marcaine Spinal

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.

4.3 Contraindications

Hypersensitivity to the active substance, amide-type local anaesthetic agents or to any of the excipients listed in section 6.1. Diseases of the central nervous system (e.g. meningitis, tumours, poliomyelitis, cranial haemorrhage). Local suppurative infections at or near the injection site. Spinal stenosis and active disease (e.g. spondylitis, tumour, tuberculosis) or spinal trauma (e.g. fracture).
Septicaemia. Pernicious anaemia with subacute degeneration of the spinal cord.
Spinal anaesthesia should not be given to patients in shock. Spinal anaesthesia should also not be given to patients with coagulation disorders or to patients with on-going anticoagulation treatment.

4.4 Special warnings and precautions for use

There should be awareness that spinal anaesthesia can sometimes lead to major blockades with paralysis of intercostal muscles and the diaphragm, especially in pregnant women.

Caution should be exercised in patients with grade II or III AV block since local anaesthetic agents can decrease the conduction capacity of the myocardium. The elderly and patients with severe hepatic disease, severely impaired renal function or whose general condition is impaired also require special attention.

Patients being treated with class III antiarrhythmic agents (e.g. amiodarone) should be closely monitored and ECG monitoring considered since the cardiac effects of bupivacaine and class III antiarrhythmic agents may be additive.

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.

Like all local anaesthetic agents, bupivacaine may cause acute toxic effects on the central nervous system and cardiovascular system when its use leads to high blood concentrations. This applies especially after accidental intravascular administration or administration into highly vascularised areas.

Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported in connection with high systemic concentrations of bupivacaine. However, high systemic concentrations are uncommon at the doses normally used in spinal anaesthesia.

One uncommon, but serious, side effect in spinal anaesthesia is extensive or total spinal blockade resulting 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 may 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 the late stages of pregnancy. Therefore, the dose should be reduced in these patients.

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

4.5 Interaction with other medicinal products and other forms of interaction

Bupivacaine should be used with caution with other local anaesthetic agents or medicinal products structurally similar to local anaesthetic agents, i.e. class IB antiarrhythmic agents, as the toxic effects are additive.

Specific interaction studies have not been performed with local anaesthetic agents and class III antiarrhythmic agents (e.g. amiodarone), but caution is recommended. (See also section 4.4 Special warnings and precautions for use).

4.6 Pregnancy and lactation

Pregnancy
No known risks for the foetus when used during pregnancy. However, note that the dose should be reduced for patients in the late stages of pregnancy (see also section 4.4 Special warnings and precautions for use).

Breast-feeding
Bupivacaine passes into breast milk, but the risk of an effect on the child seems unlikely at therapeutic doses.

4.7 Effects on ability to drive and use machines

Depending on the dose and method of administration, bupivacaine may have a transient effect on mobility and coordination.

4.8 Undesirable effects

Side effects caused by the medicinal product itself can be difficult to distinguish from the physiological effects of the nerve blockade (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 cerebrospinal leakage (e.g. post-dural-puncture headache).

For information about symptoms and treatment of acute systemic toxicity, see section 4.9 Overdose.

Very common (>1/10)	*General*: Nausea *Circulation*: Hypotension, bradycardia
Common (>1/100)	*CNS*: Post-dural-puncture headache *GI:* Vomiting *Urogenital*: Urinary retention, urinary incontinence
Uncommon	*CNS*: Paraesthesia, paresis, dysaesthesia *Musculoskeletal*: Muscle weakness, back pain
Rare (<1/1000)	*Circulation*: Cardiac arrest *General*: Allergic reactions, anaphylactic shock *CNS*: Accidental total spinal blockade, paraplegia, paralysis, neuropathy, arachnoiditis *Airways*: Respiratory depression

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

In addition, you can report to Perrigo via the following address:
www.perrigo-pharma.co.il

4.9 Overdose

Acute systemic toxicity:

Bupivacaine can cause acute toxic effects on the central nervous and cardiovascular systems if given at high doses, particularly if administered intravascularly. However, the dose used in spinal anaesthesia is low and thus the risk of overdose is unlikely. However, when administered concomitantly with other local anaesthetic agents, systemic toxic effects may occur since the toxic effects are additive.

Treatment

In the event of total spinal blockade, ensure adequate ventilation (clear airways, oxygen, if necessary intubation and controlled ventilation). In the event of a fall in blood pressure/bradycardia, administer a vasopressor, preferably with an inotropic effect.

If signs of acute systemic toxicity occur, the administration of local anaesthetic agents should be stopped immediately. Treatment must be given to maintain good ventilation, oxygen supply and circulation.

Always give oxygen. If necessary, perform intubation and controlled ventilation (possibly with hyperventilation). In the event of convulsions, give diazepam. In the event of bradycardia, give atropine. In the event of circulatory shock, give intravenous fluids, dobutamine and if necessary noradrenaline (initially 0.05 μg/kg/min, increased if needed by
0.05 μg/kg/min every 10 minutes), guided by haemodynamic monitoring in more severe cases. Ephedrine can also be tried. In the event of circulatory arrest, resuscitation measures may be indicated for several hours. Treat any acidosis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Local anaesthetics
ATC code: N01B B01

Marcaine Spinal contains bupivacaine, which is a long-acting amide local anaesthetic agent. 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 cardiac muscle.

Marcaine Spinal is intended for spinal anaesthesia. The relative density of the solution for injection is 1.004 at 20ºC (equivalent to 1.000 at 37ºC) and distribution is only marginally affected by gravity.

In spinal administration, a small dose is given, which leads to a relatively low concentration and short duration. Marcaine Spinal (without glucose) produces a less predictable blockade, but with a longer duration compared to Marcaine Spinal Heavy (with glucose).

5.2 Pharmacokinetic properties

Bupivacaine is highly lipid soluble with an oil/water distribution coefficient of 27.5.

Bupivacaine displays complete and biphasic 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 a 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, produces relatively low peak plasma concentrations (approx. 0.4 mg/ml per 100 mg injected).

After intravenous administration, total plasma clearance is approx. 0.58 l/min, the steady-state volume of distribution 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 entirely in the liver, predominantly by 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 blood flow and the activity of the metabolising enzyme.

Bupivacaine crosses the placenta and the concentration of unbound 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.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the safety evaluation other than what has already been included the summary of product characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

8 mg sodium chloride, sodium hydroxide/hydrochloric acid (to pH 5.0–6.5), water for injections to 1 ml.

6.2 Incompatibilities

Additives to spinal solutions are not recommended.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials
The solution should be used straight after the packaging has been opened.

6.4 Special precautions for storage

Store below 25ºC.

Do not freeze.

6.5 Nature and contents of container

Glass ampoules: 5 x 4 ml
The glass ampoule is marked with two colour codes around the neck of the ampoule as follows:
Upper colour ring:
orange Lower colour
ring: orange

The ampoules are in sterile blister packaging.

6.6 Special precautions for disposal and other handling

The solution should be used straight after the ampoule has been opened.

7. MANUFACTURER

Cenexi, Fontenay Sous Bois, France, for Aspen.

8. REGISTRATION HOLDER

Perrigo Israel Agencies Ltd., 1 Rakefet St., Shoham

9. MARKETING AUTHORISATION NUMBER

116-40-25503

The content of this leaflet was approved by the Ministry of Health in January 2010 and updated according to the guidelines of the Ministry of Health in June 2018.

5.5.20