

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

**Marcaine Spinal 0.5%**

Solution for injection

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

*1 ml solution for injection contains: 5 mg bupivacaine hydrochloride*

Excipient 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 physicians with experience of regional anaesthesia or under the supervision of such a physician. The lowest possible dose for adequate anaesthesia should be sought.

The doses given below are guidelines for adults. The dose must be adjusted for the individual patient.

The dose must be reduced in the elderly patients and 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.) |
|---|---------|----------|--|---------------------------------------|
| 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<sub>3</sub>-L<sub>4</sub> intervertebral space.

There is currently no clinical experience of doses higher than 20 mg. Intravenous access must be established prior to administration of Marcaine Spinal.

A spinal injection must not be given until the subarachnoid space has been clearly identified via lumbar puncture (clear cerebrospinal fluid exits via the spinal needle or is seen on aspiration). In the case of failed anaesthesia only one new attempt should be made to administer the medicinal product, which should be given at a different level and

with a smaller volume. One reason for lack of effect may be poor intrathecal distribution of the medicinal product, which may be rectified by adjusting the position of the patient

### **4.3 Contraindications**

Hypersensitivity to the active substance, amide-type local anaesthetics or to any of the excipients listed in section 6.1. Central nervous system disorders (e.g. meningitis, tumours, poliomyelitis, cranial haemorrhage). Local abscess at or near the injection site. Spinal stenosis and active spinal disease (e.g. spondylitis, tumour, tuberculosis) or spinal trauma (e.g. fracture).

Blood poisoning. Pernicious anaemia with subacute degeneration of the spinal cord. Spinal anaesthesia must not be given to patients in a state of shock. Spinal anaesthesia must not be given to patients with coagulation disorders or to patients currently undergoing anticoagulation therapy.

### **4.4 Special warnings and precautions for use**

It should be noted that spinal anaesthesia can sometimes cause major blockade with paralysis of intercostal muscles and diaphragm, particularly in pregnant women.

Caution should be observed in patients with AV block II or III, as local anaesthetics may decrease myocardial transmittance. The elderly and patients with severe hepatic disease, severe renal impairment or poor general health also require particular attention.

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

Intrathecal anaesthesia can lead to hypotension and bradycardia. The risk of such effects can be reduced by e.g., injection of a vasopressor. Hypotension should be treated immediately with administration of an intravenous sympathomimetic and repeated if required.

Like all local anaesthetics, bupivacaine may cause acute toxic effects in the central nervous and cardiovascular systems if use results in high blood concentrations. This applies particularly after inadvertent intravascular administration or administration to 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 unusual at the doses normally used for spinal anaesthesia.

An uncommon but serious, undesirable effect of spinal anaesthesia is widespread or total spinal blockade resulting in cardiovascular and respiratory depression. The cardiovascular depression is caused by extensive sympathetic blockade which may result in hypotension and bradycardia, or even cardiac arrest. Respiratory depression can be caused by blockade of the nerve supply to the respiratory muscles, including the diaphragm.

There is an increased risk of widespread or total spinal blockade in older patients and patients in the late stages of pregnancy. The dose should therefore be reduced for these patients.

In rare cases, spinal anaesthesia may cause neurological damage, resulting in paresthesia, anaesthesia, motor weakness and paralysis. It is not believed that neurological conditions such as multiple sclerosis, hemiplegia, paraplegia and neuromuscular disturbances are negatively affected by spinal anaesthesia, but caution should be observed.

This medicine contains less than 1 mmol (23 mg) of sodium per mL, i.e. it is almost “sodium free”.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Bupivacaine should be used with caution in combination with other local anaesthetics or medicinal products that are structurally similar to local anaesthetics, i.e. class IB antiarrhythmics, as the toxic effects are additive.

No specific interaction studies have been carried out for local anaesthetics and class III antiarrhythmics (e.g. amiodarone), but caution is recommended (See also section 4.4 Special warnings and precautions for use).

#### **4.6 Pregnancy and lactation**

##### *Pregnancy*

There are no known risks for the foetus when used during pregnancy. Note, however, that the dose must be reduced for patients in the late stages of pregnancy (see also section 4.4 Special warnings and precautions for use).

##### *Breastfeeding*

Bupivacaine is excreted into breast milk, but the risk of impact on the child is considered 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**

Undesirable effects caused by the medicinal product itself may be difficult to distinguish from the physiological effects of nerve blockade (e.g. hypotension, bradycardia, transient urinary retention), cases caused directly by the needle stick (e.g. spinal hematoma) or caused indirectly by the needle stick (e.g. meningitis, epidural abscess) or cases associated with cerebrospinal leakage (e.g. postdural puncture headache).

For information on the symptoms and treatment of acute systemic toxicity, refer to section 4.9 Overdose.

|                        |  |
|------------------------|--|
| Very common<br>(>1/10) | <i>General disorders:</i> Nausea<br><i>Circulation disorders:</i> Hypotension, bradycardia   |
| Common                 | <i>Nervous system disorders:</i> Postdural puncture headache<br><i>Gastrointestinal disorders:</i> Vomiting<br><i>Renal and urinary disorders:</i> Urinary retention, urinary incontinence |
| Uncommon               | <i>Nervous system disorders:</i> Paraesthesia, paresis, dysesthesia<br><i>Musculoskeletal and connective tissue disorders:</i> Muscle weakness, back pain                                  |
| Rare (<1/1000)         | <i>Circulation disorders:</i> Cardiac arrest   |

|   |
|---|
| <p><i>General disorders:</i> Allergic reactions, anaphylactic shock<br/><i>Nervous system disorders:</i> Involuntary total spinal blockade, paraplegia, paralysis, neuropathy, arachnoiditis<br/><i>Respiratory, thoracic and mediastinal disorders:</i> Respiratory depression</p> |
|---|

#### 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>

Additionally, you can report to Padagis via the following address: [Padagis.co.il](https://padagis.co.il)

## **4.9 Overdose**

### ***Acute systemic toxicity:***

When given at a high dose and particularly when administered intravascularly, bupivacaine can cause acute toxic effects of a central nervous system or cardiovascular character. However, the dose used in spinal anaesthesia is low, and thus the risk of overdose is unlikely. Systemic toxic effects may arise, however, when administered concurrently with other local anaesthetics due to the additive nature of the toxic effects.

### ***Treatment***

Adequate ventilation (free airways, oxygen, and intubation and controlled respiration if required) must be ensured in the case of total spinal blockade. In the case of a fall in blood pressure or bradycardia, administer a vasopressor, preferably with inotropic effect.

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

Oxygen must always be administered. Where required, intubation and controlled ventilation (possibly with hyperventilation). In the case of cramps: diazepam. In the case of bradycardia: atropine. In the case of circulatory failure: intravenous fluids, dobutamine and possibly noradrenaline (initially 0.05 µg/kg/min, to be increased when required by 0.05 µg/kg/min every 10 minutes); in severe cases under guidance of haemodynamic monitoring. Ephedrine can also be tested. In case of circulatory arrest, resuscitation measures over several hours may be warranted. 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-type local anaesthetic. Bupivacaine reversibly blocks impulse transmission in nerves by inhibiting the transport of sodium ions over the nerve cell 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 20°C (equivalent to 1.000 at 37°C) and the distribution is only marginally affected by gravity.

When administered to the spine, a small dose is given; this leads to a relatively low concentration and a short duration of action. Marcaine Spinal (without glucose) results in a less predictable blockade but has a longer duration compared with Marcaine Spinal Heavy (with glucose).

## **5.2 Pharmacokinetic properties**

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

Bupivacaine demonstrates total and biphasic absorption from the subarachnoid space. The half-lives of the two phases are approx. 50 and 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 that following 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 maximal plasma concentration (approx. 0.4 mg/ml per injected 100 mg).

Following intravenous administration, the total plasma clearance is approx. 0.58 l/min, the volume of distribution at steady state is 73 l, the elimination half-life is 2.7 hours, and the hepatic extraction ratio is approx. 0.40. Bupivacaine is almost entirely metabolised in the liver, particularly through aromatic hydroxylation to 4-hydroxy-bupivacaine and N-dealkylation to PPX, both of which are mediated by cytochrome P450 3A4. Clearance is therefore dependent on the hepatic blood flow and the activity of the metabolising enzyme.

Bupivacaine crosses the placenta and the concentration of unbound mepivacaine in the mother and foetus is equalised. However, the total plasma concentration will be lower in the foetus, due to a lower degree of protein binding.

## **5.3 Preclinical safety data**

There is no preclinical safety data of relevance to the safety assessment additional to that which has already been taken into consideration in the summary of product characteristics.

# **6 PHARMACEUTICAL PARTICULARS**

## **6.1 List of excipients**

Sodium chloride 8 mg, 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.  
Leftover content to be discarded.

## **6.4 Special precautions for storage**

Store below 25°C.

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 coloured ring: orange

Lower coloured ring: orange

The ampoules are packed in a sterile blister pack.

#### **6.6 Special precautions for disposal and other handling**

The solution should be used immediately after opening the ampoule.

### **7. MANUFACTURER**

Cenexi, Fontenay Sous Bois, France, for Aspen.

### **8. REGISTRATION HOLDER**

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

### **9. MARKETING AUTHORISATION NUMBER**

116.40.25503

Revised in April 2023 according to MOH guidelines.

20.4.2023