SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bupivacaine S.A.L.F. spinal 5mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains:
5 mg bupivacaine hydrochloride
(equivalent to 5.28 mg bupivacaine hydrochloride monohydrate or 4.44 mg Bupivacaine base).

Excipient with known effect:
Each 1 ml of solution contains:
3.18 mg of Sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution free of visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Spinal anaesthesia for surgery.

4.2. Posology and method of administration

Bupivacaine S.A.L.F. spinal 5mg/ml 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 L3-L4 intervertebral space.
There is currently no clinical experience of doses higher than 20 mg. Intravenous access must be established prior to administration of Bupivacaine S.A.L.F. spinal 5mg/ml.
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.

Important information about some of the excipients:
This medicine contains less than 1 mmol (23 mg) of sodium per mL, that is to say essentially “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 antiarrhytmics (e.g. amiodarone), but caution is recommended (See also section 4.4).

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).

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.

Very common (>1/10)	*General disorders:* Nausea. *Circulation disorders:* Hypotension, bradycardia.
Common (>1/100, <1/10)	*Nervous system disorders*: Postdural puncture headache. *Gastrointestinal disorders:* Vomiting *Renal and urinary disorders*: Urinary retention, urinary incontinence
Uncommon (≥1/1,000, <1/100)	*Nervous system disorders:* Paraesthesia, paresis, dysesthesia. *Musculoskeletal and connective tissue disorders:* Muscle weakness, back pain.
Rare (≥1/10,000, <1/1,000)	*Circulation disorders:* Cardiac arrest. *General disorders*: Allergic reactions, anaphylactic shock. *Nervous system disorders:* Involuntary total spinal blockade, paraplegia, paralysis, neuropathy, arachnoiditis. *Respiratory, thoracic and mediastinal disorders*: Respiratory depression.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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.

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: N01BB01
Bupivacaine S.A.L.F. spinal 5mg/ml 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.
Bupivacaine S.A.L.F. spinal 5mg/ml 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.
Bupivacaine S.A.L.F. spinal 5mg/ml (without glucose) results in a less predictable blockade but has a longer duration compared with other bupivacaine formulations 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 litre/min, the volume of distribution at steady state is 73 litre, 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, Hydrochloric acid/ Sodium hydroxide 1N (q.s to pH 4.0 –6.5), Water for injections.

6.2. Incompatibilities

Additives to spinal solutions are not recommended.
In the absence of compatibility studies, this solution must not be mixed with other medicinal products.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions, however, it is recommended to store at room temperature. Do not freeze.

6.5. Nature and contents of container

Colourless type I glass ampoule.
Each pack contains 5 ampoules of 10 ml.

6.6. Special precautions for disposal and other handling

The solution contains no preservatives and are intended for single use only. They should be used immediately after opening.
Any unused residual solution should be discarded.
Any unused product or waste material should be disposed of in accordance with the local requirements.

7. Marketing authorization Holder and Importer

RAZ PHARMACEUTICS LTD.,
31 Gesher Haetz, Industrial Park, Emek Hefer, Israel

8. MARKETING AUTHORISATION NUMBER

176-38-37223-99

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