

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bupivacain Sintetica 5 mg/ml hyperbar

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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, e.g. urological and lower limb surgery, lasting 2-3 hours, abdominal surgery lasting 45-60 minutes.

4.2. Posology and method of administration

Bupivacain Sintetica 5 mg/ml hyperbar 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 and the dose must be adjusted for the individual patient.

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

Indication	Dose ml	Dose mg	Onset time minutes (approx.)	Duration hours (approx.)
Urological surgery	1.5-3 ml	7.5-15 mg	5-8 min	2-3 hours
Surgery in the lower extremities, 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 is in the L3-L4 intervertebral space.

There is currently no clinical experience of doses higher than 20 mg.

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 disease (e.g. spondylitis, tumour, tuberculosis) or trauma (e.g. spinal 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 blockades involving paralysis of the 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 elderly 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 millilitre, 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 human 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 block (e.g. fall in blood pressure, bradycardia, transient urinary retention), cases caused directly by the needle puncture (e.g. spinal hematoma) or caused indirectly by the needle puncture (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 (>1/10)	<i>General disorders:</i> Nausea <i>Cardiac disorders:</i> Hypotension, bradycardia
Common (>1/100)	<i>Nervous system disorders:</i> Postdural puncture headache <i>Gastrointestinal disorders:</i> Vomiting <i>Renal and urinary disorders:</i> Urinary retention, urinary incontinence
Uncommon	<i>Nervous system disorders:</i> Paraesthesia, paresis, dysesthesia <i>Musculoskeletal and connective tissue disorders:</i> Muscle weakness, back pain
Rare (<1/1,000)	<i>Cardiac disorders:</i> Cardiac arrest <i>General disorders:</i> Allergic reactions, anaphylactic shock <i>Nervous system disorders:</i> Involuntary total spinal blockade, paraplegia, paralysis, neuropathy, arachnoiditis <i>Respiratory, thoracic and mediastinal disorders:</i> 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>

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

Bupivacain Sintetica 5 mg/ml hyperbar 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.

Bupivacain Sintetica 5 mg/ml hyperbar 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 in the subarachnoid space is significantly 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. Bupivacain (without glucose) results in a less predictable blockade but has a longer duration compared with Bupivacain Sintetica 5 mg/ml hyperbar (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 maximum 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 bupivacaine 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

Glucose monohydrate for injection, sodium hydroxide and/or hydrochloric acid (to pH 4.0–6.0), water for injection.

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 is to be discarded.

6.4. Special precautions for storage

Store below 30°C.

Keep in the original package to protect from light

Do not freeze.

6.5. Nature and contents of container

Glass ampoules: 10 x 5 ml

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

Sintetica SA, Via Penate 5, CH-6850 Mendrisio, Switzerland

8. REGISTRATION HOLDER

CTS Ltd

4 HAHARASH ST.,HOD-HASHARON 4524075

9. MARKETING AUTHORISATION NUMBER

174-92-37021-99

Approved in 12/2023 by the MOH..