

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bupivacaine Spinal Tung Grindeks 5 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 5 mg of bupivacaine hydrochloride (as anhydrous).

- 5.28 mg bupivacaine hydrochloride monohydrate equivalent to 5 mg bupivacaine hydrochloride anhydrous;
- anhydrous glucose, corresponding to 80 mg glucose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

A clear, colourless solution free from visible particles.

pH of solution is 4.0 to 6.0.

Osmolality: 460-486 mosmol/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Invented name] is indicated for adults and children of all ages.

Spinal anaesthesia in surgical and obstetric interventions, for example urological surgery and surgery in lower limbs lasting 2-3 hours and abdominal surgeries lasting 45-60 minutes.

4.2 Posology and method of administration

[Invented name] should only be used by a physician experienced in regional anaesthesia or under their supervision. The lowest dose required for adequate anaesthesia should be used.

The dosages in the following table 1 are recommended as a guide for use in the average adult. Individual variations in onset and duration occur. For elderly and in patients in late stages of pregnancy, these doses should be reduced.

Table 1 Dosage recommendations

Indication	Dose ml	Dose mg	Onset time min (approx.)	Duration hours (approx.)
Urological surgery	1.5-3 ml	7.5-15 mg	5-8 min	2-3 hours
Surgery in lower limbs, including hip surgery	2-4 ml	10-20 mg	5-8 min	2-3 hours

Indication	Dose ml	Dose mg	Onset time min (approx.)	Duration hours (approx.)
Abdominal surgery (including caesarean section)	2-4 ml	10-20 mg	5-8 min	45-60 min

Clinical experience of doses higher than 20 mg is not currently available.

Spinal injection should only be performed after the subarachnoid space has been clearly identified via lumbar puncture (clear cerebrospinal fluid comes out via the spinal needle or is seen during aspiration). If the anaesthesia fails, only one fresh attempt should be made to administer the medicine at a different level of the spinal cord, using a smaller volume of the medicinal product. A reason for inadequate effect may be poor medicinal distribution intrathecally. If the anaesthesia appears inadequate, a change in patient position may improve the distribution of the medical product.

Neonates, infants and children up to 40 kg
[Invented name] can be used in children.

One of the differences between small children and adults is the relatively high CSF volume in infants and neonates, requiring a relatively larger dose/kg to produce the same level of block compared to adults.

Paediatric regional anaesthesia procedures should be performed by qualified clinicians who are familiar with this population and the techniques.

The doses in the table should be regarded as guidelines for use in paediatric patients. Individual variations occur. Standard textbooks should be consulted for factors affecting specific block technique and for individual patient requirements. The lowest dose required for adequate anaesthesia should be used.

Dosage recommendations in neonates, infants and children

Body weight (kg)	Dose (mg/kg)
< 5	0.40-0.50 mg/kg
5-15	0.30-0.40 mg/kg
15-40	0.25-0.30 mg/kg

Method of administration

For intrathecal use only. Recommended site of injection is below L3.

4.3 Contraindications

- Hypersensitivity to the active substance, to amide-type local anaesthetics or to any of the excipients listed in section 6.1.

General contraindications related to intrathecal anaesthesia should be taken into account:

- Acute active disease of the central nervous system such as meningitis, tumours, poliomyelitis, intracranial hemorrhage
- Pyogenic infection of the skin at or adjacent to the site of lumbar puncture.
- Spinal stenosis and active disease (e.g. spondylitis, tumour, tuberculosis) or recent trauma (e.g. fracture of the vertebral column).
- Septicaemia.
- Pernicious anaemia with subacute combined degeneration of the spinal cord.
- Cardiogenic or hypovolaemic shock and cardiac insufficiency.

- Coagulation disorders or ongoing anticoagulant treatment.

4.4 Special warnings and precautions for use

Intrathecal anaesthesia should only be performed by clinicians with the necessary knowledge and experience.

Regional or local anaesthetic procedures should always be performed in a properly equipped and staffed area. Resuscitative equipment and medicines should be immediately available, and the anaesthetist should remain in constant attendance.

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

Caution should be exercised in patients with AV block II or III as local anaesthetics may reduce the conductivity of the myocardium.

Patients in poor general condition due to ageing or other compromising factors such as advanced liver or renal dysfunction require special attention.

Patients treated with anti-arrhythmic medicines class III (e.g. amiodarone) should be kept under close surveillance and ECG monitoring considered, since cardiac effects may be additive.

Intrathecal anaesthesia can cause hypotension and bradycardia. The risk of such effects can be reduced, for example, by injecting a vasopressor. Hypotension should be treated immediately intravenously with a sympathomimetic, repeated as necessary.

Bupivacaine can, like all local anaesthetics, cause acute toxicity effects on the central nervous and cardiovascular systems, with use resulting in high blood concentrations. This is especially the case after unintentional intravascular administration or injection into highly vascular areas.

Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported in connection with high systemic concentrations of bupivacaine. High systemic concentrations are not expected with normal doses used for intrathecal anaesthesia.

Rare, but serious adverse effect in spinal anaesthesia is extended or total spinal block that results in cardiovascular depression and respiratory depression. The cardiovascular depression is caused by extensive sympathetic block that can result in hypotension and bradycardia, or even heart failure. Respiratory depression can be caused by blockade of the innervation of the respiratory muscles, including the diaphragm.

There is an increased risk of high or total spinal blockade, resulting in cardiovascular and respiratory depression, in the elderly and in patients in the late stages of pregnancy. The dose should therefore be reduced in these patients.

In rare cases spinal anaesthesia can cause neurological injury with paraesthesia, anaesthesia, motor weakness and paralysis as consequence. Occasionally these injuries are permanent. Neurological disorders, such as multiple sclerosis, hemiplegia, paraplegia and neuromuscular injuries is assumed not to be negatively affected by intrathecal anaesthesia but requires caution. Before treatment is initiated the benefit risk ratio should be evaluated.

Sodium

This medicine contains less than 1 mmol of sodium (23 mg) per ampoule, 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 patients receiving other local anaesthetics or medicinal products that are structurally similar to amide-type local anaesthetics, i.e. Class IB anti-arrhythmics, as the toxic effects are additive.

Specific interaction studies with local anaesthetics and class III antiarrhythmics (e.g. amiodarone) have not been carried out caution is recommended. (See also 4.4 Special warnings and precautions for use).

4.6 Pregnancy and breast-feeding

Pregnancy

It is reasonable to assume that a large number of pregnant women and women of childbearing age have been given bupivacaine.

No specific disturbances to the reproductive process have so far been reported, e.g. no increased incidence of malformations (See also section 5.2. Pharmacokinetic properties).

However, note that the dose should be reduced by 20-30% for patients in the late stages of pregnancy due to the risk of neonatal respiratory depression, hypotension and bradycardia. (See also section 4.4).

Bupivacaine transfers across to the placenta. Although the concentration of bupivacaine in the umbilical cord are lower than in the mother's serum concentrations, the free bupivacaine concentrations will remain the same.

Breast-feeding

Bupivacaine is excreted in the mother's milk in small quantities and it is poorly absorbed orally, thus adverse effects in breastfed infants are not anticipated. It is therefore possible to breastfeed after anaesthesia with bupivacaine. Based on the latest literature data mothers with normal term or older infants generally can breastfeed as soon as they are awake, stable and alert. However, care should be given to premature infants and infants at risk for apnoea, hypotonia or hypotension, who could be more sensitive to small amounts of bupivacaine and therefore should be closely observed, particularly in the first 24 hours after bupivacaine application to the mother.

Fertility

No human data on the effect of bupivacaine on fertility are available.

4.7 Effects on ability to drive and use machines

Besides the direct anaesthetic effect, local anaesthetics may have a very mild effect on mental function and co-ordination even in the absence of obvious CNS-toxicity and may temporarily impair motor ability and alertness.

4.8 Undesirable effects

Summary of the safety profile

Side effects caused by the product per se are difficult to distinguish from the physiological effects of the nerve block (e.g. decrease in blood pressure, bradycardia, temporary urinary retention), events caused directly (e.g. spinal haematoma) or indirectly (e.g. meningitis, epidural abscess) by the needle puncture or events associated to cerebrospinal leakage (e.g. postdural puncture headache).

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

Tabulated list of adverse reactions

The frequencies of adverse events are ranked according to the following: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) or not known (cannot be estimated from the available data).

System organ class	Frequency	Adverse reaction
Immune system disorders	Rare	Allergic reactions, anaphylactic shock
Nervous system disorders	Common	Postdural puncture headache
	Uncommon	Paraesthesia, paresis, dysaesthesia
	Rare	Total spinal block (unintentional), paraplegia, paralysis, neuropathy, arachnoiditis
Cardiac disorders	Very common	Hypotension, Bradycardia
	Rare	Cardiac arrest
Respiratory, thoracic and mediastinal disorders	Rare	Respiratory depression
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting
Renal and urinary disorders	Common	Urine retention, urine incontinence
Musculoskeletal and connective tissue disorders	Uncommon	Muscle weakness, back pain

Paediatric population

Adverse reactions in children are similar to those in adults, but in children early signs of local anaesthetic toxicity may be difficult to discover in cases where the block is given under sedation or general anaesthesia.

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. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

Acute systemic toxicity

Bupivacaine can cause acute toxic effects of central nervous and cardiovascular nature if given in high doses, especially if administered intravascularly. If the medicine is used as recommended, it is not likely to cause blood levels high enough to cause systemic toxicity. However, if other local anaesthetics are concomitantly administered, toxic effects are additive and may cause systemic toxic reactions. Systemic adverse reactions are characterised by numbness of the tongue, light-headedness, dizziness and tremors, followed by convulsions and cardiovascular disorders.

Treatment of acute systemic toxicity

If signs of acute systemic toxicity or total spinal blockade appear, injection of the local anaesthetic should be immediately stopped.

CNS symptoms (convulsion, CNS depression) must promptly be treated with appropriate airway/respiratory support and the administration of anticonvulsants (barbiturates or benzodiazepines).

If circulatory arrest should occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation, ventilation and circulatory support as well as treatment of metabolic acidosis are of vital importance. In the event of cardiac arrest, a successful outcome may require prolonged resuscitative efforts and appropriate treatment should be provided according to advanced life support guidelines/protocols. Administration of intravenous 20% lipid emulsion should be considered soon after airway management.

If cardiovascular depression (hypotension, bradycardia) occurs, appropriate treatment with intravenous fluids, a vasopressor, and / or inotropic agents should be considered. Children should be given doses commensurate with age and weight.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Local anaesthetics, ATC code: N01B B01

[Invented name] 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 heart muscle.

[Invented name] 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 spread in the subarachnoid space is markedly affected by gravity.

In spinal administration, a small dose is given which leads to a relatively low concentration and short duration. Bupivacaine Spinal (without glucose) gives a less predictable block, but with a longer duration compared to [Invented name] (with glucose).

5.2 Pharmacokinetic properties

Bupivacaine has high lipid solubility. The oil/water partition coefficient is 27.5.

Bupivacaine exhibits complete and biphasic absorption from the subarachnoid space with half-lives for both phases of about 50 and about 400 minutes, with large variations. The slow absorption 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, results in a relatively low maximum plasma concentration (approximately 0.4 mg/ml per 100 mg injected).

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

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

The pharmacokinetics in children are similar to those in adults.

5.3 Preclinical safety data

Based on conventional studies of safety pharmacology, acute and subchronic toxicity, non-clinical data reveal no special hazard other than those already reported elsewhere in this document.

The mutagenic and carcinogenic potential of bupivacaine has not been determined. Bupivacaine crosses the placenta. In reproduction toxicity studies, decreased survival of the offspring of rats and embryoletality was noted in rabbits at bupivacaine doses, which were five- or nine-fold the maximum recommended daily dose in humans. A study in rhesus monkeys suggested altered postnatal behaviour following exposition to bupivacaine (epidural infusion) at birth.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose monohydrate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Additives to spinal solutions are not recommended.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Hydrolytic class colourless borosilicate glass ampoules with one point cut. The ampoules are packed in a liner and placed into carton box.
Pack size: 5 ampoules.

6.6 Special precautions for handling and disposal

The solution must be used immediately after opening.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE SUMMARY OF PRODUCT

2022-10-05