Instructions for Use Leaflet: Information for the User

BUPISEN 2.5 mg/ml solution for injection
BUPISEN 5 mg/ml solution for injection
BUPISEN 5 mg/ml hyperbaric solution for injection
BUPISEN 7.5 mg/ml hyperbaric solution for injection
BUPISEN 10 mg/ml hyperbaric solution for injection
Bupivacaine hydrochloride
Generic Medicine

Please read this leaflet carefully before using this medicine, as it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not give it to anyone else, even if their symptoms are the same as yours, as this could be dangerous.
- If you experience any side effects, including those not listed in this leaflet, please speak to your doctor, pharmacist or nurse. See section 4.

Contents of this leaflet:
1. What BUPISEN is and what it is used for
2. What you need to know before using BUPISEN
3. How to use BUPISEN
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1. What BUPISEN is and what it is used for

BUPISEN contains the active ingredient bupivacaine hydrochloride and belongs to a group of medicines called local anaesthetics, which are used before surgery to induce anaesthesia.

BUPISEN can be used to induce peripheral anaesthesia (local, trunk, and loco-regional infiltration, sympathetic block, sacral epidural, spinal-subarachnoid infiltration).

BUPISEN is indicated, either alone and in combination with other anaesthetic medicines, for the following procedures:
- general surgery;
- bone and joint surgery (orthopaedics);
- eyes (ophthalmology);
- ear and throat (otorhinolaryngology);
- oral cavity (stomatology);
- genitals and during childbirth (obstetrics and gynaecology);
- skin (dermatology).

2. What you need to know before using BUPISEN

You must not be given BUPISEN:
- if you are allergic to bupivacaine hydrochloride, to similar substances (amide-type anaesthetics) or to any of the other ingredients of this medicine (listed in section 6);
- if you are to undergo a type of anaesthesia near a regional vein (Bier Block);
- *if you suffer from diseases of the central nervous system (meningitis, tumours, poliomyelitis, intracranial haemorrhages, spinal stenosis), spinal diseases (spondylitis, tuberculosis, tumours) or if you have recently suffered trauma (fractures);*
- *if you suffer from infections characterised by the presence of bacteria in the blood (septicaemia);*

- *if you have a vitamin B12 deficiency (pernicious anaemia), associated with spinal cord problems (subacute spinal cord degeneration);*
- *if you have a bacterial skin infection (pyogenic) at the injection site or in the surrounding area;*
- *if you have experienced a cardiac arrest (cardiogenic shock) or if you have a reduced blood volume due to hemorrhage or fluid loss (hypovolemic shock);*
- *if you have a bleeding disorder or are taking medicines used to prevent blood clots (anticoagulants).*

BUPISEN 7.5 mg/ml hyperbaric solution for injection is not to be used for epidural anaesthesia during childbirth (obstetric epidural anaesthesia).

Warnings and Precautions
Consult your doctor, pharmacist or nurse before BUPISEN is administered to you.

In the case of epidural anaesthesia or peripheral nerve block, this medicine must be administered under the direct supervision of a doctor, as serious side effects may occur, such as:
- cardiac arrest, and death; *these effects may occur particularly with the use of BUPISEN 7.5 mg/ml hyperbaric solution for injection*.

Furthermore, during treatment with BUPISEN, problems affecting the central nervous system, the heart and blood vessels (cardiovascular problems, ventricular arrhythmias, ventricular fibrillation, or sudden cardiovascular collapse) and death may occur when this medicine is present in high concentrations in the blood, particularly when accidentally administered into the bloodstream (intravascularly) or into areas rich in blood vessels (highly vascularised areas). When BUPISEN is used at the recommended doses, the quantities of this medicine in the blood do not reach high levels.

Following the use of similar medicines (local anaesthetics), serious side effects, including death, have been reported. Therefore, this medicine will only be administered to you under the close supervision of a doctor and specialist staff, and in facilities equipped with the necessary emergency equipment for urgent treatment.

This medicine must be administered with great caution and under close medical supervision if:
- you are elderly or debilitated;
- you suffer from heart problems (partial or complete heart block), as this medicine may reduce the heart's contractility (cardiac conduction);
- you have advanced liver disease or severe impairment of kidney function;
- you are in the final stages of pregnancy;
- you have a reduced blood volume (hypovolaemia), as this medicine, when used during intrathecal anaesthesia, may cause a severe and sudden drop in blood pressure (hypotension);
- you are taking medicines used to treat heart rhythm disorders (class III antiarrhythmics), such as amiodarone. In this case, your doctor may decide to monitor your heart function (electrocardiogram);
- you suffer from disorders of the nervous system (multiple sclerosis, hemiplegia, paraplegia) or of the nerves and muscles (neuromuscular disorders);
- you have suffered trauma to the joints (major intra-articular injury) or have undergone joint surgery, and BUPISEN is to be administered intra-articularly;
- you have reduced heart and blood vessel function (reduced cardiovascular function), and BUPISEN is to be administered epidurally;
- you are taking medicines used to treat mood disorders (MAOIs, tricyclic antidepressants);
- you are due to undergo a type of anaesthesia known as a stellate ganglion block.

Your doctor will monitor you closely during treatment with this medicine, as certain anaesthetic techniques can cause side effects, some of which may be serious:
- **epidural anaesthesia or central nerve block** may lead to changes in heart and blood vessel function (cardiovascular depression), particularly if there is already a reduction in blood volume (hypovolaemia. In addition, a drop in blood pressure (hypotension) and a slow heart rate (bradycardia) may occur. A drop in blood pressure may require immediate intravenous administration of medicines used to stimulate the heart (sympathomimetics);

- **stellate ganglion block** may cause side effects similar to those of central nervous system block, as well as cardiac toxicity with an increase or decrease in heart rate, potentially leading to cardiac arrest;
- **injections into the eyes (retrobulbar)** may lead to very rare cases of temporary loss of vision (temporary blindness), cardiac and circulatory failure (cardiovascular collapse), breathing difficulties (apnoea) and convulsions, all of which must be treated immediately;
- **injections into the eyes (retrobulbar) or around the eyes (peribulbar)** may cause long-lasting disturbances of the eye muscles; therefore, the lowest possible doses and concentrations of anaesthetic must be used;
- **paracervical block** may result in a reduction or increase in the foetal heart rate (bradycardia/tachycardia). Therefore, the foetal heart rate must be monitored whilst this medicine is being used;
- **spinal anaesthesia**: total or high spinal block may occur, leading to cardiac and circulatory failure (cardiovascular depression) and respiratory failure (respiratory depression). These effects are more likely to occur if you are elderly or in the late stages of pregnancy; in such cases, the dose must be reduced;
- **intrathecal anaesthesia**: brain damage (paraesthesia, numbness, motor weakness and paralysis) may rarely occur, which in some cases may be permanent.

If you require local anaesthesia in areas such as the fingers or the base of the penis, you will be given bupivacaine without adrenaline to prevent tissue damage (ischaemic necrosis).

Before using this medicine, your doctor will check your blood circulation.
Your doctor may decide to use a test dose of this medicine, in combination with adrenaline, to prevent accidental intravenous or intrathecal injection.
During administration, your doctor will monitor you closely and will stop treatment immediately at the first sign of any warning symptoms, such as changes in sensation or drowsiness (sensory disturbances).

Rare cases of serious reactions have been reported, even in non-allergic people; therefore, when using this medicine, equipment, medicines and specialist staff must be immediately available for emergency treatment.

Children
The safety and efficacy of Bupisen in children under 1 year of age have not been established. Only limited data are available.
In epidural anaesthesia, the dose must be adjusted according to child's weight and age.

Other medicines and BUPISEN
Tell your doctor, pharmacist or nurse if you are using, have recently used or might use any other medicines.

Use this medicine with caution and tell your doctor if you are taking:
- other medicines used to relieve pain during surgery (amide-type local anaesthetics, such as lidocaine);
- medicines similar to BUPISEN, such as medicines used to treat heart rhythm disorders, mexiletine and tocainide;
- medicines used to treat depression (MAOIs, tricyclic antidepressants).

Pregnancy and Breast-feeding
If you are pregnant, think you might be pregnant, are planning to become pregnant, or are breastfeeding, ask your doctor or pharmacist for advice before using this medicine.

Pregnancy
If you are in the late stages of pregnancy, the dose for spinal anaesthesia must be reduced.
Paracervical anaesthesia is associated with an increased risk of adverse effects on the foetus (see Warnings and Precautions).

Breast-feeding
Use this medicine with caution if you are breastfeeding, as BUPISEN passes into breast milk in small quantities.

Driving vehicles and using machinery
BUPISEN impairs the ability to drive vehicles and operate machinery.
BUPISEN may cause mild disturbances to mental function and control of movements (coordination). If you experience these symptoms, avoid driving and using machinery.

BUPISEN 2.5 mg/ml and 5 mg/ml solution for injection contains sodium
This medicine contains 3.15 mg/ml (0.137 mmol/ml) of sodium. This should be taken into account in people with reduced kidney function or who are on a low sodium diet.

3. How to use BUPISEN

This medicine will be administered to you by a doctor or qualified healthcare professional during surgical procedures. If you have any doubts, consult your doctor, pharmacist or nurse.

The dose and method of administration will be determined by your doctor based on your needs and age.
The vials and syringes do not contain any preservatives and are for single-use only; any remaining medicine must be discarded.

Use in adults and children over 12 years of age
The dose should be the lowest possible that achieves adequate anaesthesia; the recommended dose ranges from 2-3 mg to 100-150 mg.
Do not exceed the maximum dose of 150 mg, corresponding to 30 ml of the 5 mg/ml solution and 60 ml of the 2.5 mg/ml solution.

Use in children aged 1 to 12 years
Your doctor will adjust the dose according to the child's weight.

If you use more BUPISEN than you should
Accidental injection into a blood vessel may cause toxic effects within a few seconds or minutes.
Following the administration of an excessive dose of this medicine, toxic effects (systemic toxic reactions) may occur within 15-60 minutes after the injection.
It is unlikely that BUPISEN, hyperbaric solution, when administered under the recommended conditions, will cause general toxicity. However, if other medicines similar to BUPISEN, hyperbaric solution, are administered at the same time, the toxic effects may be cumulative.

In the event of accidental use or ingestion of an excessive dose of this medicine, contact your doctor immediately or go to the A&E department of your nearest hospital.

If you forget to use BUPISEN
This medicine will be administered to you by a doctor or nurse, so it is unlikely that you will miss a dose.

If you have any doubts about the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all other medicines, this medicine may cause side effects, although not all people will experience them.

The following side effects may occur:

Very common (may affect more than 1 in 10 people):

- low blood pressure (hypotension);
- nausea.

Common (may affect up to 1 in 10 people):
- sensory disturbances in the legs and arms or other parts of the body (paraesthesia), dizziness, headache (following spinal tap, *post-dural puncture headache*);
- slowed heart rate (bradycardia);
- increased blood pressure (hypertension);
- vomiting;
- inability to empty the bladder (urinary retention), involuntary loss of urine (*urinary incontinence*).

Uncommon (may affect up to 1 in 100 people):
- central nervous system toxicity: convulsions, abnormal sensations around the mouth (perioral paraesthesia), numbness of the tongue, intolerance to sounds (hyperacusis), visual disturbances, loss of consciousness, tremor, light-headedness, ringing in the ears (tinnitus), speech difficulties (dysarthria), *disorders affecting the contraction of one or more muscles (paresis), sensory disturbance (dysesthesia)*;
- *muscle weakness, back pain*.

Rare (may affect up to 1 in 1,000 people):
- allergic reactions, severe allergic reaction (anaphylactic shock);
- inflammation of the nerves (neuropathy), nerve damage (peripheral nerve damage), inflammation of the membrane surrounding the brain and spinal cord (arachnoiditis), loss of the ability to contract one or more muscles (paresis), movement and sensation disorders in the lower limbs (paraplegia), total (unintentional) spinal block, *reduced or lost ability to contract one or more muscles (paralysis)*.
- *double vision (diplopia)*;
- cardiac arrest, heart rhythm disturbances (cardiac arrhythmias);
- breathing difficulties (respiratory depression).

Unknown (frequency cannot be estimated from the available data)
- agitation, disorientation, dilated pupils (mydriasis), increased metabolism and body temperature, contraction of the masticatory muscles (trismus), sweating, increased respiratory rate (tachypnoea), dilation of the bronchi (bronchodilation), increased blood vessel calibre (vasodilation);
- allergic reactions with local manifestations such as skin irritation (urticaria, pruritus) or systemic bronchial muscle contraction (bronchospasm).

Reporting side effects
If you experience any side effects, including those not listed in this leaflet, consult your doctor, pharmacist or nurse. You may also report side effects directly via the national reporting system at https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store BUPISEN

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date printed on the pack. The expiry date refers to the last day of that month.
This medicine does not require any special storage conditions.

Do not dispose any of medicines in the drain or with household waste. Ask your pharmacist how to dispose of medicines you no longer use. This will help protect the environment.

6. Contents of the pack and other information

What BUPISEN 2.5 mg/ml solution for injection contains?
- The active substance is bupivacaine hydrochloride: 1 ml of solution contains 2.5 mg of bupivacaine hydrochloride.
- The other ingredients are: sodium chloride, water for injections.

What BUPISEN 5 mg/ml solution for injection contains?
- The active substance is bupivacaine hydrochloride: 1 ml of solution contains 5 mg of bupivacaine hydrochloride.
- The other ingredients are: sodium chloride, water for injections.

What BUPISEN 5 mg/ml hyperbaric solution for injection contains?
- *The active substance is bupivacaine hydrochloride: 4 ml of solution contain 20 mg of bupivacaine hydrochloride.*
- *The other ingredients are: glucose, water for injections.*

What BUPISEN 7.5 mg/ml hyperbaric solution for injection contains?
- *The active substance is bupivacaine hydrochloride: 3 ml of solution contain 22.5 mg of bupivacaine hydrochloride.*
- *The other ingredients are: glucose, water for injections.*

What BUPISEN 10 mg/ml hyperbaric solution for injection contains?
- *The active substance is bupivacaine hydrochloride: 2 ml of solution contain 20 mg of bupivacaine hydrochloride.*
- *The other ingredients are: glucose, water for injections.*

Description of the appearance of BUPISEN and contents of the pack

BUPISEN 2.5 mg/ml and 5 mg/ml solution for injection:
Box of 10 vials of 1 ml, 2 ml, 5 ml, or 10 ml.
Box of 5 vials of 20 ml.
Pack containing 1 pre-filled single-use syringe of 5 ml or 10 ml.

BUPISEN 5 mg/ml hyperbaric solution for injection:
Sterile pack containing 1 vial of 4 ml.

BUPISEN 7.5 mg/ml hyperbaric solution for injection:
Sterile pack containing 1 vial of 3 ml.

BUPISEN 10 mg/ml hyperbaric solution for injection:
Sterile pack containing 1 vial of 2 ml.

Marketing Authorisation Holder and Manufacturer
Industria Farmaceutica Galenica Senese - Via Cassia Nord 351 - Monteroni d'Arbia (SI)

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The following information is intended solely for doctors or healthcare professionals.

Special warnings and precautions for use
Adults and children over 12 years of age
Dosage and method of administration

BUPISEN is usually administered in minimal doses, varying according to the indication, from 2–3 mg to 100–150 mg, as indicated for guidance in the table below:

Type of anaesthesia	Dosage Concentration (mg/ml)	ml	mg
Trigeminal block	2.5 5	1-5 0.5-4	2.5-12.5 2.5-20
Axillary block	2.5 5	20-40 10-30	50-100 50-150
Stellate ganglion block	2.5	10-20	25-50
Intercostal block	2.5 5 The dose is for each intercostal space	4-8 3-5	10-20 15-25
Epidural	2.5 5	30-40 10-20	75-100 50-100
Continuous epidural	2.5 5 Start with 10 ml, then 3-5-8 ml every 4-6 hours, depending on the segments to be anaesthetised and the patient's age		
Sacral block	2.5 5	15-40 15-20	37.5-100 75-100
Splanchnic block	2.5	10-40	25-100
Lumbar sympathetic block	2.5	10-40	25-100
Pelvic block	5	20-30	100-150
Spinal subarachnoid	*10* *7.5* 5	*2* *2.6* 4	*20* *20* 20

Warning: Since they do not contain paraseptic excipients, the vials and syringes must be used for a single administration only. Any remaining product must be discarded.
The maximum dose for an adult per single administration should not exceed 150 mg, corresponding to 30 ml of the 5 mg/ml solution and 60 ml of the 2.5 mg/ml solution. More generally, the safety dose that should not be exceeded, in both adults and children, is 2 mg/per a single administration.
In prolonged analgesic therapy, doses ranging from 0.25 to 1 mg/kg of body weight are usually used; administration may be repeated 2-3 times within 24 hours.
N.B. When performing prolonged blocks involving successive bolus administrations, the risk of reaching toxic plasma concentrations or of inducing local neuronal damage must be taken into account.

The dose to be administered must be calculated based on the doctor's experience and knowledge of the patient's clinical condition. The lowest possible doses capable of achieving adequate anaesthesia should be used. Individual variations may occur in terms of onset and duration of action. The extent of anaesthetic diffusion can be difficult to predict, as it is influenced by the quantity of medicine administered, particularly in the case of isobaric solutions.

To prevent accidental intravascular injection, aspiration should be carried out before and during administration of the main dose, which must be injected slowly or in increasing doses. During the procedure, the patient’s vital signs must be monitored closely and verbal contact maintained. Where epidural anaesthesia is required, it is recommended that a test dose of 3-5 ml of bupivacaine with adrenaline be administered first. An accidental intravascular injection can be recognised by a temporary increase in heart rate; an accidental intrathecal injection is recognised by signs of spinal block. At the first sign of toxicity, stop administration immediately.

The specific weight of Bupisen 2.5 mg/ml and 5 mg/ml is 1.006 at 20°C, and 0.997 at 37°C.
Any overdose of the anaesthetic must be avoided, and two maximum doses must never be administered without an interval of at least 24 hours.
In any case, the lowest possible doses and concentrations that achieve the desired effect should be used.

BUPISEN 5 mg/ml hyperbaric solution for injection
Newborns, infants and children over 40 kg.
BUPISEN 5 mg/ml hyperbaric solution may be used in children. One of the differences between young children and adults is the relatively high volume of cerebrospinal fluid (CSF) in infants and newborns, which requires a relatively higher dose per kg to produce the same level of block as in adults.

Paediatric regional anaesthesia procedures must be performed by qualified doctors who are familiar with this patient group and with the technique.
The doses given in the table below should be regarded as guidelines for paediatric use. Individual variations may occur.
Reference texts should be consulted both regarding factors affecting specific block techniques and regarding the individual needs of the patient.
The lowest dose necessary to achieve adequate anaesthesia should be used.

Recommended dose in newborns, infants and children

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

For further information, please refer to the Summary of Product Characteristics.