SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BUPISEN 2.5 mg/mL solution for injection
1 mL ampoules; 2 mL ampoules; 5 mL ampoules; 10 mL ampoules; 20 mL ampoules; 5 mL pre-filled syringe; 10 mL pre-filled syringe

BUPISEN 5 mg/mL solution for injection
1 mL ampoules; 2 mL ampoules; 5 mL ampoules; 10 mL ampoules; 20 mL ampoules; 5 mL pre-filled syringe; 10 mL pre-filled syringe

BUPISEN 5 mg/mL hyperbaric solution for injection
4 mL ampoule

BUPISEN 7.5 mg/mL hyperbaric solution for injection
3 mL ampoule

BUPISEN 10 mg/mL hyperbaric solution for injection
2mL ampoule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BUPISEN 2.5 mg/mL solution for injection

Active ingredient:	1mL ampoule	2mL ampoule	5mL ampoule and pre-filled syringe	10mL ampoule and pre-filled syringe	20mL ampoule
Bupivacaine hydrochloride	2.5 mg	5 mg	12.5 mg	25 mg	50 mg

BUPISEN 5 mg/mL solution for injection

Active ingredient:	1mL ampoule	2mL ampoule	5mL ampoule and pre-filled syringe	10mL ampoule and pre-filled syringe	20mL ampoule
Bupivacaine hydrochloride	5 mg	10 mg	25 mg	50 mg	100 mg

BUPISEN 5 mg/mL hyperbaric solution for injection

Active ingredient:	*4 mL ampoule*
Bupivacaine hydrochloride	*20 mg*

BUPISEN 7.5 mg/mL hyperbaric solution for injection

Active ingredient:	*3 mL ampoule*
Bupivacaine hydrochloride	*22.5 mg*

BUPISEN 10 mg/mL hyperbaric solution for injection

Active ingredient:	*2mL ampoule*
Bupivacaine hydrochloride	*20 mg*

For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
BUPISEN may be used for all types of peripheral anaesthesia:
- local infiltration, peripheral nerve block and regional anaesthesia
- sympathetic nerve block
- epidural and caudal anaesthesia
- spinal (subarachnoid) anaesthesia.

BUPISEN is therefore indicated for all procedures in general surgery, orthopaedic surgery, ophthalmic surgery, otorhinolaryngological surgery, dental surgery, obstetric and gynaecological surgery, and dermatological surgery, either used alone or in combination with general anaesthesia.

4.2 Posology and method of administration
Adults and children over 12 years of age
BUPISEN is usually administered at the lowest effective doses, varying according to the indication, from 2–3 mg to 100–150 mg, as shown for guidance in the table below:

Type of anaesthesia	Dose 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 expressed per 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 An initial dose of 10 mL is administered, followed by 3–5–8 mL every 4–6 hours, depending on the segments to be anaesthetised and the patient's age		
Caudal 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 preservative excipients, the ampoules and syringes are intended for single administration only. Any remaining solution must be disposed of.

The maximum dose in adults for a 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 maximum safe dose, which should not be exceeded in both adults and children, is 2 mg/kg per single administration.
In prolonged analgesic therapy, doses ranging from 0.25 to 1 mg/kg body weight are usually used; administration may be repeated 2–3 times within 24 hours.
Note: When prolonged blocks are performed using repeated bolus administrations, the risk of reaching toxic plasma concentrations or causing local neuronal injury should be considered.

The dose to be administered should be calculated based on the physician's experience and knowledge of the patient's clinical condition. The lowest effective doses that provide adequate anaesthesia should be used. Individual variations may occur with regard to the onset and duration of action. The extent of spread of anaesthesia may be difficult to predict, as it is influenced by the volume of medicinal product administered, particularly in the case of isobaric solutions.

To prevent accidental intravascular injection, aspiration should be performed before and during administration of the main dose, which should be injected slowly or in incremental doses. During the procedure, the patient's vital signs must be closely monitored and verbal contact must be maintained. If 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 transient increase in heart rate; an accidental intrathecal injection is recognised by signs of spinal block. At the first sign of toxicity, administration must be discontinued immediately (see Section 4.8, Treatment of Acute Systemic Toxicity).
The specific gravity 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 of the anaesthetic must never be administered without a minimum interval of 24 hours.
In any case, the lowest doses and concentrations that allow the desired effect to be achieved should be used.

BUPISEN 5 mg/mL hyperbaric solution for injection
Neonates, infants, and children weighing more than 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 neonates, which requires a relatively higher dose per kg to produce the same level of block as in adults.

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

Recommended dose in neonates, 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*

4.3 Contraindications
Hypersensitivity to the active ingredient, to any of the excipients, or to other chemically related substances, in particular local anaesthetics of the same group (amide type).
The product is also contraindicated in intravenous regional anaesthesia (Bier block), as accidental release of bupivacaine into the circulation may result in acute systemic toxic reactions.
The use of bupivacaine 7.5 mg/mL is contraindicated in epidural anaesthesia in obstetrics (see Sections 4.4 and 4.6).

General contraindications should be considered in cases of intrathecal anaesthesia:
- active acute diseases of the central nervous system, such as meningitis, tumours, poliomyelitis, and intracranial haemorrhage
- spinal stenosis and active disease of the spine (e.g., spondylitis, tuberculosis, tumour) or recent trauma (e.g., fractures)
- septicaemia
- pernicious anaemia associated with subacute combined degeneration of the spinal cord
- pyogenic skin infection at the injection site or in the surrounding area
- cardiogenic or hypovolaemic shock
- coagulation disorders or ongoing anticoagulant treatment.

4.4 Special warnings and precautions for use
The total dosage must be adjusted according to the patient's general condition, age, and relevant medical history.
Cases of cardiac arrest or death have been reported following the use of bupivacaine for epidural anaesthesia or peripheral nerve block. In some cases, resuscitation has been difficult or impossible despite apparently adequate preparation and appropriate management by the personnel involved. *In the majority of cases, this has occurred following the use of the 7.5 mg/mL solution.*

Intrathecal anaesthesia should only be performed by, or under the supervision of, physicians with the necessary competence and experience.

Bupivacaine, like all local anaesthetics, when used in local anaesthetic procedures resulting in high blood concentrations of the drug, may cause acute toxic effects involving the central nervous system and the cardiovascular system, particularly following accidental intravascular administration or injection into highly vascularised areas. Following high systemic concentrations of bupivacaine, ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse, and death have been reported. *However, at the doses normally used for intrathecal anaesthesia, high systemic concentrations are not expected.*

Regional anaesthesia procedures must always be performed in appropriately equipped areas by qualified personnel. Immediate availability of the equipment and drugs necessary for monitoring and emergency resuscitation must be ensured.
In patients undergoing major blocks or receiving high doses of the drug, an intravenous catheter should be inserted before administration of the local anaesthetic. The physician must have undergone full and adequate training in the procedure to be used and must be experienced in the diagnosis and management of adverse reactions, systemic toxicity, or other complications (see sections 4.8 and 4.9).
Major peripheral nerve blocks may involve the administration of a large volume of local anaesthetic into highly vascularised areas, often close to large blood vessels where there is an increased risk of intravascular injection and/or rapid systemic absorption, which may result in high plasma concentrations.
Although regional anaesthesia is frequently the anaesthetic technique of choice, some patients require special attention to reduce the risk of serious adverse effects:

- elderly or debilitated patients;
- patients with partial or complete heart block, as local anaesthetics may depress cardiac conduction;
- patients with advanced liver disease or severe impairment of renal function;
- patients in advanced stages of pregnancy;
- *hypovolaemic patients may develop severe and sudden hypotension during intrathecal anaesthesia, regardless of the local anaesthetic used. Hypotension generally occurs following intrathecal block in adults;*
- patients receiving Class III antiarrhythmic drugs (e.g., amiodarone) should be closely monitored, and ECG monitoring should be considered, as cardiac effects may be additive.

Some local anaesthetic techniques may be associated with severe adverse reactions, regardless of the local anaesthetic used:
-Central nerve blocks: may cause cardiovascular depression, particularly in the presence of hypovolaemia. Epidural anaesthesia should therefore be used with caution in patients with impaired cardiovascular function;
-Retrobulbar injections: may, in very rare cases, reach the cerebral subarachnoid space, causing temporary blindness, cardiovascular collapse, apnoea, convulsions, etc. Such reactions must be diagnosed and treated immediately;
-Retrobulbar and peribulbar injections of local anaesthetics: are associated with a low risk of persistent ocular muscle dysfunction. Primary causes include trauma and/or local toxic effects affecting muscles and/or nerves. The severity of such tissue reactions is related to the extent of trauma, the concentration of local anaesthetic, and the duration of tissue exposure to the local anaesthetic. As with all local anaesthetics, the lowest doses and concentrations that achieve the desired effect should be used. Vasoconstrictors may aggravate tissue reactions and should only be used when indicated.

Local anaesthetics, even at low doses, when injected into the head and neck, such as during stellate ganglion block procedures, may produce systemic toxicity due to inadvertent intra-arterial injection or intravascular or subarachnoid absorption.

-Paracervical block: may occasionally cause foetal bradycardia/tachycardia. Careful monitoring of foetal heart rate is therefore necessary.
-Continuous intra-articular infusion is not an approved indication for Bupisen. However, post-marketing cases of chondrolysis have been reported exclusively in North America in patients receiving continuous postoperative intra-articular infusion of local anaesthetics. The majority of reported cases of chondrolysis involved the shoulder joint. A causal relationship has not been established.

A rare but serious adverse reaction following spinal anaesthesia is total or high spinal block, with subsequent cardiovascular and respiratory depression. Cardiovascular depression is caused by extensive sympathetic blockade resulting in profound hypotension and bradycardia or even cardiac arrest. Respiratory depression may be caused by blockade of the innervation of the respiratory muscles, including the diaphragm. The risk of total or high spinal block is greater in elderly patients and in patients in advanced stages of pregnancy. The dose should therefore be reduced in these patients (see Sections 4.3 and 4.6).

The occurrence of neurological injury is a rare consequence of intrathecal anaesthesia and may result in paraesthesia, anaesthesia, motor weakness, and paralysis. Such injuries are occasionally permanent.

Caution is recommended in patients with neurological disorders such as multiple sclerosis, hemiplegia, paraplegia, and neuromuscular disorders, although intrathecal anaesthesia is not considered to adversely affect these conditions. Before initiating treatment, consideration should be given to whether the benefits outweigh the possible risks for the patient.

Epidural anaesthesia may cause hypotension and bradycardia. The risk may be reduced by preloading the circulation with crystalloid or colloid solutions. Hypotension must be treated immediately with the administration, which may be repeated, of an intravenous sympathomimetic agent. In children, the dosage should be adjusted according to age and body weight.

When bupivacaine is administered intra-articularly, caution is recommended when recent major intra-articular trauma is suspected or when surgery has resulted in extensive exposure of the joint, as this may accelerate absorption and result in higher plasma concentrations.

If local anaesthetic infiltration is to be performed in areas lacking collateral circulation (e.g., fingers, the base of the penis), as a precautionary measure the anaesthetic should be used without a vasoconstrictor to reduce the risk of ischaemic necrosis. If moderate ischaemia is desired, Bupisen 0.50% Solution for Injection with adrenaline may be used. The product should be used with extreme caution in patients receiving monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants. Prior to administration, the physician should assess the patient's circulatory status. The use of an appropriate test dose, preferably containing adrenaline, is recommended to allow for the prompt detection of inadvertent intravascular or intrathecal injection. The anaesthetic solution should be injected cautiously in small doses, approximately 10 seconds after aspiration. Particularly when highly vascularised areas are to be infiltrated, it is recommended to wait approximately 2 minutes before proceeding with the actual locoregional block.

The patient should be kept under close observation, and administration must be discontinued immediately at the first warning sign (e.g., changes in sensorium).

Appropriate resuscitation equipment, emergency medications, and personnel trained in emergency management must be immediately available, as serious reactions, sometimes with fatal outcome, have been reported in rare cases following the administration of local anaesthetics, even in the absence of a history of individual hypersensitivity.

Paediatric population
The safety and efficacy of Bupisen in children under 1 year of age have not been established. Only limited data are available.
The use of bupivacaine for intra-articular block in children aged 1 to 12 years has not been documented.
The use of bupivacaine for major nerve block in children aged 1 to 12 years has not been documented.
In children, epidural anaesthesia should be administered in incremental doses appropriate to their age and body weight, as thoracic epidural anaesthesia in particular may cause severe hypotension and respiratory insufficiency.

4.5 Interactions with other medicinal products and other forms of interactions
Bupivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, such as certain antiarrhythmics (e.g., lidocaine, mexiletine, and tocainide), since their systemic toxic effects are additive. Caution is advised in patients receiving Class III antiarrhythmic agents (e.g., amiodarone), despite the absence of specific interaction studies with this class of drugs (see Section 4.4).
The product should be used with extreme caution in patients receiving monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants.

4.6 Pregnancy and Breast-feeding
Pregnancy
A large number of pregnant women and women of childbearing potential are estimated to have received bupivacaine. To date, no specific disturbances to the reproductive process have been reported (e.g., no increased incidence of congenital malformations; see also Section 5.2). *In patients in advanced stages of pregnancy, the dose for spinal anaesthesia must be reduced (see also Section 4.4).*

Adverse effects on the foetus due to local anaesthetics, such as foetal bradycardia, appear to be more pronounced with paracervical block. These effects may be due to high concentrations of the anaesthetic reaching the foetus.

Breastfeeding
As with other local anaesthetics, bupivacaine may be excreted into breast milk; however, the amount excreted is so small that there is generally no risk to the neonate.

4.7 Effects on ability to drive and use machines
Bupisen may affect the ability to drive vehicles or operate machinery.
In addition to their direct anaesthetic effect, local anaesthetics may have a very mild effect on mental function and coordination, even in the absence of overt central nervous system toxicity, and may temporarily impair locomotion and alertness.

4.8 Adverse reactions
General
The adverse reaction profile of Bupisen is comparable to that of other long-acting local anaesthetics. Adverse drug reactions are difficult to distinguish from the physiological effects of the nerve block itself

(such as decrease in blood pressure, bradycardia, and temporary urinary retention), and from events caused directly by the injection (e.g., nerve fibre trauma, spinal haematoma), indirectly (e.g., epidural abscess and meningitis), or associated with cerebrospinal fluid leakage (e.g., post-dural puncture headache). Neurological injury is a rare but well-recognised complication of regional anaesthesia, particularly epidural and spinal anaesthesia.

Table of adverse reactions to Bupisen

Very common (≥1/10)	Vascular disorders: hypotension Gastrointestinal disorders: nausea.
Common (≥1/100, < 1/10)	Nervous system disorders: paraesthesia, dizziness, post-dural puncture headache Cardiac disorders: bradycardia Vascular disorders: hypertension Gastrointestinal disorders: vomiting Renal and urinary disorders: urinary retention, urinary incontinence.
Uncommon (≥1/1.000, <1/100)	Nervous system disorders: signs and symptoms of central nervous system toxicity (convulsions, circumoral paraesthesia, numbness of the tongue, hyperacusis, visual disturbances, loss of consciousness, tremor, light-headedness, tinnitus, dysarthria, paresis, dysesthesia) *Musculoskeletal and connective tissue disorders: muscle weakness, back pain.*
Rare (<1/1.000)	Immune system disorders: allergic reactions, anaphylactic reactions/shock Nervous system disorders: neuropathy, peripheral nerve injury, arachnoiditis, paresis, paraplegia, unintended total spinal block, paralysis. *Eye disorders: diplopia* Cardiac disorders: cardiac arrest, cardiac arrhythmias Respiratory, thoracic and mediastinal disorders: respiratory depression.

Other adverse reactions reported include manifestations of central nervous system stimulation (excitement, disorientation, mydriasis, increased metabolism and body temperature, trismus, sweating, tachypnoea, bronchodilation, vasodilation) and allergic reactions with local manifestations (urticaria, pruritus) or systemic manifestations (bronchospasm).

Acute systemic toxicity

Systemic toxic reactions primarily involve the central nervous system and the cardiovascular system. These reactions are caused by high blood concentrations of the local anaesthetic following accidental intravascular injection, overdose, or exceptionally rapid absorption from highly vascularised areas (see section 4.4). Central nervous system reactions are comparable to those of other amide-type local anaesthetics, whereas cardiac reactions depend to a greater extent, both quantitatively and qualitatively, on the drug.

Under the recommended conditions of use, Bupisen Iperbarica is unlikely to produce blood concentrations sufficiently high to cause systemic toxicity. However, if other local anaesthetics are administered concomitantly, their toxic effects are additive and may result in systemic toxicity.

Central nervous system toxicity develops gradually, with symptoms and signs of increasing severity. The initial symptoms are generally circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis, tinnitus, and visual disturbances. Dysarthria, muscle twitching, or tremors are more severe manifestations that precede the onset of generalised convulsions. These signs should not be mistaken for neuroexcitatory manifestations. Loss of consciousness and convulsive seizures may follow, lasting from a few seconds to several minutes.
Following convulsions, hypoxaemia and hypercapnia develop rapidly as a result of increased muscular activity, impaired respiration, and possible loss of airway patency. In severe cases, apnoea may occur. Acidosis, hyperkalaemia, hypocalcaemia, and hypoxaemia increase and potentiate the toxic effects of local anaesthetics.

The patient's return to the initial clinical condition results from redistribution of the local anaesthetic away from the central nervous system, followed by its subsequent metabolism and excretion. Recovery may be rapid provided that large amounts of the medicinal product have not been administered.

In severe cases, **cardiovascular** effects may occur, generally preceded by signs of central nervous system toxicity. In patients who are deeply sedated or undergoing general anaesthesia, cardiovascular effects may occur in the absence of prodromal central nervous system effects. As a result of high systemic concentrations of local anaesthetics, hypotension, bradycardia, arrhythmias, and even cardiac arrest may occur. In rare cases, however, cardiac arrest has occurred without preceding central nervous system prodromal effects.

Paediatric population
Adverse drug reactions in children are similar to those observed in adults; however, in children, early signs of systemic local anaesthetic toxicity may be difficult to detect when the block is administered during general anaesthesia.

Treatment of acute systemic toxicity
Administration of the local anaesthetic must be discontinued immediately if signs of acute systemic toxicity or total spinal block appear. Symptoms of central nervous system toxicity (convulsions, central nervous system depression) must be treated immediately with appropriate support of airway patency and respiration, together with the administration of anticonvulsants, such as diazepam at a dose of 10–20 mg intravenously; barbiturates are not recommended, as they may exacerbate medullary depression. Circulation may be supported by the intravenous administration of corticosteroids at appropriate doses; diluted solutions of alpha- and beta- adrenergic agonists with vasoconstrictor activity (mephentermine, metaraminol, and others) or atropine sulphate may also be added.

If circulatory arrest occurs, cardiopulmonary resuscitation must be initiated immediately. It is of vital importance to ensure optimal oxygenation, support ventilation and circulation, and treat acidosis.

If cardiovascular depression occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressors, inotropic agents, and/or lipid emulsion should be considered. In children, the dosage should be adjusted according to age and body weight.

If cardiac arrest occurs, prolonged resuscitation efforts may be required to achieve a favourable outcome.

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: https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

4.9 Overdose
Accidental intravascular injection of local anaesthetics may cause immediate systemic toxic reactions (within a few seconds to several minutes). In the event of overdose, systemic toxicity appears later (15–60 minutes after injection) due to a slower increase in blood concentrations of the local anaesthetic (see section 4.8 “Acute systemic toxicity” and “Treatment of acute systemic toxicity”).
Under the recommended conditions of use, Bupisen Iperbarica is unlikely to produce blood concentrations sufficiently high to cause systemic toxicity. However, if other local anaesthetics are administered concomitantly, their toxic effects are additive and may result in systemic toxicity (see section 4.8 “Acute systemic toxicity” and “Treatment of acute systemic toxicity”).

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic category: local anesthetics - amides
ATC Code: N01BB01.
Bupivacaine hydrochloride (BUPISEN) is a long-acting amide-type local anaesthetic.
Bupivacaine administered for intrathecal anaesthesia has a rapid onset of action and a medium-to-long duration of anaesthetic effect.

The onset and duration of the local anaesthetic effect of bupivacaine depend on the dose and site of administration.

Like other local anaesthetics, bupivacaine reversibly blocks nerve conduction and prevents the influx of sodium ions through the nerve fibre cell membrane. The sodium channel of the nerve fibre membrane is considered the receptor upon which local anaesthetics act.

Local anaesthetics may have similar effects on other excitable membranes, such as those of the brain and myocardium. Excessive systemic concentrations of the drug may result in symptoms and signs of toxicity, primarily affecting the central nervous and cardiovascular systems.

Central nervous system toxicity occurs at lower plasma concentrations and generally precedes cardiovascular effects (see section 4.8 “Treatment of acute systemic toxicity”). The direct effects of local anaesthetics on the myocardium include slowed conduction, negative inotropy, and cardiac arrest.

Indirect cardiovascular effects (hypotension, bradycardia) may occur following epidural administration and are related to the extent of the concomitant sympathetic block.

Bupisen Iperbarica 5 mg/mL, Bupisen Iperbarica 7.5 mg/mL and Bupisen Iperbarica 10 mg/mL are hyperbaric solutions (relative to cerebrospinal fluid) and their initial diffusion into the intrathecal space is influenced by gravity. Considering the low dose administered, intrathecal distribution results in relatively low drug concentrations, and the duration of the local anaesthetic effect tends to be relatively short. Compared with hyperbaric solutions, glucose-free solutions produce less predictable levels of block, but with a longer duration.

5.2 Pharmacokinetic properties

Bupivacaine has a pKa of 8.2 and a partition coefficient of 346 (n-octanol/phosphate buffer at pH 7.4 at 25°C). The pharmacological activity of the metabolites is lower than that of bupivacaine.
The plasma concentration of bupivacaine depends on the dose, route of administration, and vascularity of the injection site.

Bupivacaine exhibits complete and biphasic absorption from the epidural space, with half-lives of approximately 7 minutes and 6 hours, respectively. *Hyperbaric bupivacaine also exhibits complete and biphasic absorption from the subarachnoid space, with half-lives of approximately 50 and 408 minutes for the two phases.* Slow absorption is the rate-limiting factor in the elimination of bupivacaine; this explains why the apparent half-life after epidural or subarachnoid administration is longer than that after intravenous administration.
Considering the low dose required for intrathecal administration, plasma concentrations of bupivacaine after intrathecal block are low compared with those observed after other regional anaesthesia procedures. In general, the increase in maximum plasma concentration is approximately 0.4 mg/L for every 100 mg injected. This means that following administration of 20 mg, plasma concentrations would be approximately 0.1 mg/L.
Bupivacaine has a total plasma clearance of 0.58 L/min, a steady-state volume of distribution of 73 L, a terminal half-life of 2.7 hours, and an intermediate hepatic extraction ratio of 0.38 following intravenous administration. It is mainly bound to alpha-1-acid glycoprotein, with plasma binding of 96%.
Bupivacaine clearance occurs almost exclusively through hepatic metabolic processes and is more sensitive to changes in the intrinsic activity of hepatic enzymes than to hepatic perfusion.

The pharmacokinetics in children are similar to those in adults.

During continuous epidural infusion, an increase in total plasma concentrations was observed, which was associated with a postoperative increase in alpha-1-acid glycoprotein. The concentration of the unbound, pharmacologically active fraction was similar before and after surgery.

Bupivacaine rapidly crosses the placenta, and equilibrium between the bound and unbound fractions is readily achieved. The degree of plasma protein binding in the foetus appears to be lower than that observed in the mother; this probably results in a lower total plasma concentration in the foetus.

Bupivacaine is extensively metabolised in the liver, primarily via aromatic hydroxylation to 4-hydroxy-bupivacaine and via N-dealkylation to PPX, both mediated by cytochrome P450 3A4. Approximately 1% of bupivacaine is excreted as unchanged drug in the urine within 24 hours, and approximately 5% as PPX. Plasma concentrations of PPX and 4-hydroxy-bupivacaine during and after continuous administration of bupivacaine are low compared with those of the parent compound.

5.3 Preclinical safety data

Based on conventional pharmacological studies of safety pharmacology, single- and repeated-dose toxicity, reproductive toxicity, mutagenic potential, and local tolerance, no risks to humans have been identified other than those expected on the basis of the pharmacodynamic effects of high doses of bupivacaine (e.g. central nervous system signs and cardiotoxicity).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Bupisen 2.5 mg/mL solution for injection and Bupisen 5 mg/mL solution for injection:
Sodium chloride, water for injections.
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:
Glucose, water for injections.

6.2 Incompatibilities

The solubility of bupivacaine at pH values above 6.5 is limited. This should be taken into consideration when alkaline solutions, such as carbonates, are added, as precipitation may occur.

6.3 Shelf life

Bupisen 2.5 mg/mL solution for injection and Bupisen 5 mg/mL solution for injection:
2 years when stored in the original package under the recommended storage conditions.
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:
3 years when stored in the original package under the recommended storage conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Neutral glass ampoules containing 1, 2, 5 and 10 mL of 2.5 mg/mL and 5 mg/mL solution for injection, supplied in packs of 10 ampoules.
Neutral glass ampoules containing 20 mL of 2.5 mg/mL and 5 mg/mL solution for injection, supplied in packs of 5 ampoules.
Single-use pre-filled syringes containing 5 and 10 mL of 2.5 mg/mL and 5 mg/mL solution for injection, supplied in packs containing one syringe.
Neutral glass ampoule containing 4 mL of 5 mg/mL hyperbaric solution for injection, supplied in a single sterile pack.
Neutral glass ampoule containing 3 mL of 7.5 mg/mL hyperbaric solution for injection, supplied in a single sterile pack.
Neutral glass ampoule containing 2 mL of 10 mg/mL hyperbaric solution for injection, supplied in a single sterile pack.

6.6 Special precautions for disposal of the used medicinal product

The solutions do not contain preservatives, are for single use only and must be used immediately after opening. Any unused medicinal product remaining after use must be disposed of.

Bupisen ampoules must not be re-sterilised.

7. MARKETING AUTHORISATION HOLDER

Industria Farmaceutica Galenica Senese S.r.l.

8. MARKETING AUTHORISATION NUMBERS

Bupisen 2.5 mg/mL solution for injection 10 ampoules of 1 mL – A.I.C. No. 034171013;
Bupisen 2.5 mg/mL solution for injection 10 ampoules of 2 mL – A.I.C. No. 034171025;
Bupisen 2.5 mg/mL solution for injection 10 ampoules of 5 mL – A.I.C. No. 034171037;
Bupisen 2.5 mg/mL solution for injection 10 ampoules of 10 mL – A.I.C. No. 034171049;
Bupisen 2.5 mg/mL solution for injection 5 ampoules of 20 mL – A.I.C. No. 034171052;
Bupisen 2.5 mg/mL solution for injection 1 pre-filled syringe of 5 mL – A.I.C. No. 034171114;
Bupisen 2.5 mg/mL solution for injection 1 pre-filled syringe of 10 mL – A.I.C. No. 034171126;
Bupisen 5 mg/mL solution for injection 10 ampoules of 1 mL – A.I.C. No. 034171076;
Bupisen 5 mg/mL solution for injection 10 ampoules of 2 mL – A.I.C. No. 034171088;
Bupisen 5 mg/mL solution for injection 10 ampoules of 5 mL – A.I.C. No. 034171090;
Bupisen 5 mg/mL solution for injection 10 ampoules of 10 mL – A.I.C. No. 034171102;
Bupisen 5 mg/mL solution for injection 5 ampoules of 20 mL – A.I.C. No. 034171064;
Bupisen 5 mg/mL solution for injection 1 pre-filled syringe of 5 mL – A.I.C. No. 034171138;
Bupisen 5 mg/mL solution for injection 1 pre-filled syringe of 10 mL – A.I.C. No. 034171140.
Bupisen 5 mg/mL hyperbaric solution for injection 1 ampoule of 4 mL in a sterile pack
A.I.C. No. 034171227
Bupisen 7.5 mg/mL hyperbaric solution for injection 1 ampoule of 3 mL in a sterile pack
A.I.C. No. 034171215
Bupisen 10 mg/mL hyperbaric solution for injection 1 ampoule of 2 mL in a sterile pack
A.I.C. No. 034171203

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

BUPISEN 2.5 mg/mL and BUPISEN 5 mg/mL in ampoules: January 2000/January 2010
BUPISEN 2.5 mg/mL and BUPISEN 5 mg/mL in pre-filled syringes: April 2004/January 2010
BUPISEN 5 mg/mL hyperbaric solution for injection: 14/07/2009
BUPISEN 7.5 mg/mL hyperbaric solution for injection: 14/07/2009
BUPISEN 10 mg/mL hyperbaric solution for injection: 14/07/2009

10. DATE OF TEXT REVISION

5 August 2023