Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bupivacaine Heavy 5 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection contains bupivacaine hydrochloride monohydrate equivalent to 5 mg of bupivacaine hydrochloride.
Each ampoule of 4 ml contains bupivacaine hydrochloride monohydrate equivalent to 20 mg of bupivacaine hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection)
Clear and colourless solution
pH = 4.0 to 6.0
Osmolality: 420 – 520 mOsm/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bupivacaine Heavy 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 1.5-3 hours
- Lower abdominal surgeries lasting 1.5-3 hours.

4.2 Posology and method of administration

This medicinal product 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.

Posology

Adults and children or adolescents over 40 kg
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.

Table 1 Dosage recommendations

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

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 medicinal product 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.

Special populations
Elderly population
The dose should be reduced in the elderly (see section 4.4).

Other special populations
There is a potential risk to have a spinal block that is too widely spread in situations where there is elevated intra-abdominal pressure (end of pregnancy, ascites, obesity).
The dose should be reduced in these populations, by up to 20-30% in patients in the late stages of pregnancy (see sections 4.4 and 4.6).

Paediatric population
Neonates, infants and children up to 40 kg
This medicinal product 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.

Table 2 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. Must not be injected intravascularly.
The 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.
- 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. Caution should be exercised in particular for patients with preload-dependent cardiac lesions (i.e. Aortic stenosis).

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 sympathic 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.

Caution should be exercised and a careful assessment carried out before local anaesthesia in the following cases, depending upon clinician's evaluation and ability to manage potential complications:

- Patients with chronic back-pain: a careful assessment is recommended before local anaesthesia in order to detect potential contraindications for the use of local anaesthesia (i.e spinal stenosis).
- Patients with pre-existing headache: a careful assessment is recommended in order to detect potential contraindications for the use of local anaesthesia (i.e increased intracranial pressure)
- Patients with hypotension: as Bupivacaine may worsen hypotension, close monitoring and appropriate management are necessary and alternative anaesthetic options may be considered in patients with preexisting important hypotension. Bupivacaine should not be used in case of severe hypotension due to cardiogenic or hypovolaemic shock (see section 4.3).
- Persistent paresthesias: before using spinal anaesthesia, healthcare professionals should assess the patient's overall neurologic status and consider alternative approaches if persistent paresthesias are present.

Sodium
This medicinal product contains less than 1 mmol of sodium (23 mg) per dose, 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 section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

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 5.3).

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 can be used during pregnancy, if clinically needed.

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.

Fertility
No human and animal 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 itself 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.

Table 3List of adverse reactions

System Organ Class	**Very Common** ≥1/10	**Common** ≥1/100 to < 1/10	**Uncommon** ≥1/1,000 to < 1/100	**Rare** ≥1/10,000 to < 1/1,000	**Very Rare** < 1/10,000	**Not known** (cannot be estimated from the available data)
Immune system disorders				Allergic reactions, Anaphylactic shock		
Nervous system disorders		Postdural puncture headache	Paraesthesia, Paresis, Dysaesthesia	Total spinal block (unintentional), Paraplegia, Paralysis,		

				Neuropathy, Arachnoiditis		
Cardiac disorders	Bradycardia			Cardiac arrest		
Vascular disorders	Hypotension					
Respiratory, thoracic and mediastinal disorders				Respiratory depression		
Gastrointestinal disorders	Nausea	Vomiting				
Muscuskeletal and connective tissue disorders			Muskle weakness, Back pain			
Renal and urinary disorders		Urine retention, Urine incontinence				

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 HPRA Pharmacovigilance
Website: www.hpra.ie

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 medicinal product 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 anesthetics, ATC code: N01B B01

This medicinal product 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.

This medicinal product is intended for hyperbaric spinal anaesthesia. The relative density of the solution for injection is 1.026 at 20 ºC (equivalent to 1.021 at 37 ºC) 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.

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/l 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 bupivacaine 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 embryolethality was noted in rabbits at bupivacaine doses, which were several fold higher than the maximum recommended daily dose in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
This medicinal product must be used immediately after opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Glass ampoule filled with 4 ml. Each ampoule is individually packaged in a sealed blister pack with a peelable blister lid. The outside of the ampoules is sterile. Box of 5 ampoules.

6.6 Special precautions for disposal and other handling

Instruction for use:
The product should be inspected visually for particles and discoloration prior to administration. Only clear and colourless solution free from particles or precipitates should be used.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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1 Rue Alexander Fleming
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69007
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8 MARKETING AUTHORISATION NUMBER

PA1968/025/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th January 2025

10 DATE OF REVISION OF THE TEXT