SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bupivacaine Baxter 2.5 mg/ml solution for injection
Bupivacaine Baxter 5 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2.5 mg or 5 mg of bupivacaine hydrochloride.

Excipients with known effect:
Each ml of the solution contains 3.15 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Surgical anaesthesia in adults and adolescents above 12 years of age
- Acute pain management in adults, infants and children above 1 year of age

Infiltration anesthesia when prolonged duration of action is required, e.g. for post-operative pain.
Conduction anesthesia with prolonged duration or epidural anesthesia in cases where addition of epinephrine is contraindicated and severe muscle relaxation is not desirable.

4.2 Posology and method of administration

Posology

Bupivacaine Baxter should only be used by physicians experienced in regional anaesthesia or under his or hers supervision. The lowest dosage needed to provide effective anaesthesia should be administered.

In order to avoid intravascular injection, aspiration should be repeated prior to and during administration of the main dose, which should be injected slowly or in divided doses, at a rate of 25-50 mg/min, while closely observing the patient's vital functions and maintaining verbal contact.

When an epidural dose is to be injected, a preceding test dose of 3-5 ml bupivacaine containing adrenaline (epinephrine) is recommended. An inadvertent intravascular injection may be recognised by a temporary increase in heart rate and an accidental intrathecal injection by signs of a spinal block. If toxic symptoms occur, the injection should be stopped immediately.

The dosage varies and depends upon the area to be anaesthetised, the vascularity of the tissues, the number of neuronal segments to be blocked, individual tolerance and the technique of anaesthesia used.

When prolonged blocks are used, either by continuous infusion or by repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing a local neural injury must be considered.

In general, surgical anaesthesia (e.g. epidural administration) requires the use of higher concentrations and doses. When a less intense block is required, the use of a lower concentration is indicated. The volume of medicinal product used will affect the extent of spread of anaesthesia.

The dosages in the following table are recommended as a guide for use in the average adult. Individual variations in onset and duration occur. For young, elderly or debilitated patients, these doses should be reduced.

Dosage recommendations for adults

	Concentration		**Dose**		**Onset min**	**Duration hours**	**Comments**
	mg/ml	**%**	**ml**	**mg**			
Infiltration anaesthesia	2.5	0.25	≤60	≤150	1-3	3-4	
	5	0.5	≤30	≤150	1-3	4-8	
Intercostal block (per nerve up to 10 nerves in total)	5	0.5	2-3	10-15	3-5	4-8	
Major Nerve Block (e.g. epidural-, sacral- brachial plexus)	5	0.5	15-30	75-150	10-30	4-8	
Intra-Articular Block (e.g. following knee arthroscopy)	2.5	0.25	≤40	≤100	5-10	2-4 after wash out	
Thoracic epidural (surgical procedures)	2.5	0.25	5-15	12.5-37.5	10-15	1.5-2	The dose includes test dose
	5	0.5	5-10	25-50	10-15	2-3	The dose includes test dose
Lumbar epidural Postoperative pain relief	2.5	0.25	6-15	15-37.5	15-30	1-2	The dose includes test dose
Surgical procedures including Caesarean section	5	0.5	15-30	75-150	15-30	2-3	The dose includes test dose
Caudal epidural block	2.5	0.25	20-30	50-75	20-30	1-2	The dose includes test dose

Vaginal delivery and vacuum extraction	5	0.5	20-30	100-150	15-30	2-3	The dose includes test dose
	2.5	0.25	6-10	15-25			
	5	0.5	6-10	30-50			

In *continuous epidural anaesthesia* administered as intermittent doses 20 ml of Bupivacaine Baxter 2.5 mg/ml is given initially (50 mg bupivacaine hydrochloride) followed by 6-16 ml Bupivacaine Baxter 2.5 mg/ml (15-40 mg bupivacaine hydrochloride) every 2-6 hour depending on the desired number of anesthetized segments and the age of the patient.

Continuous epidural infusion (for example post operative pain management)

	Concentration		**Initial Bolus Dose[1]**		**Dose**	
	mg/ml	**%**	**ml**	**mg**	**ml**	**mg**
Lumbar epidural continuous infusion	2.5	0.25	5-10	12.5-25	5-7.5	12.5-18.75
Thoracic epidural continuous infusion	2.5	0.25	5-10	12.5-25	2.5-5	6.25-12.5
Epidural continuous infusion for vaginal delivery	2.5	0.25	6-10	15-25	2-5	5-12.5

1) If adequate bolus dose was **not** given in the previous hour.
2) Maximum recommended dose in 24 hours must not be exceeded (see below).

In combination with an opioid, the bupivacaine dose can be reduced. The patient should be regularly monitored throughout the infusion duration with respect to blood pressure, heart rate, and any toxic symptoms. If signs of toxic effects are observed the infusion should immediately be discontinued.

Maximum recommended dose
The maximum recommended dose at a single occasion is estimated using the value 2 mg/kg body weight. For adults the recommended dose is up to 150 mg bupivacaine hydrochloride within a period of four hours.
Bupivacaine Baxter 2.5 mg/ml: 60 ml (150 mg bupivacaine hydrochloride)
Bupivacaine Baxter 5 mg/ml: 30 ml (150 mg bupivacaine hydrochloride)
The dose must be determined by evaluating the size, age and physical status of the patient as well as other relevant circumstances. Maximum recommended dose in 24 hours is 400 mg.

Paediatric population 1-12 years of age

Paediatric regional anaesthetic procedures should be performed by qualified clinicians who are familiar with this population and the technique.
The doses in the table should be regarded as guidelines for use in paediatrics. Individual variations occur. In children with a high body weight a gradual reduction of the dosage is often necessary and should be based on the ideal body weight. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements. The lowest dose required for adequate analgesia should be used.

Dosage recommendations for children

	Conc. mg/ml	Volume ml/kg	Dose mg/kg	Onset min	Duration of effects hours
Acute Pain Management (pre- and Postoperative)					
Caudal Epidural Administration	2.5	0.6-0.8	1.5-2	20-30	2-6
Lumbar Epidural Administration	2.5	0.6-0.8	1.5-2	20-30	2-6
Thoracic Epidural Administration[b)]	2.5	0.6-0.8	1.5-2	20-30	2-6
Field Block (e.g., minor nerve blocks and infiltration)	2.5 5.0		0.5-2.0 0.5-2.0		
Peripheral Nerve Blocks (e.g. ilioinguinal – iliohypogastric)	2.5 5.0		0.5-2.0 0.5-2.0	a) a)	

a) The onset and duration of peripheral nerve blocks depend on the type of block and the dose administered.
b) Thoracic epidural blocks need to be given by incremental dosage until the desired level of anaesthesia is achieved.

In children, the dosage should be calculated on a weight basis up to 2 mg/kg.

In order to avoid intravascular injection, aspiration should be repeated prior to and during administration of the main dose. This should be injected slowly in incremental doses, particularly in the lumbar and thoracic epidural routes, constantly and closely observing the patient's vital functions.

Peritonsillar infiltration has been performed in children above 2 years of age with bupivacaine 2.5 mg/ml at a dose of 7.5-12.5 mg per tonsil.

Ilioinguinal-iliohypogastric blocks have been performed in children aged 1 year or older with bupivacaine 2.5 mg/ml at a dose of 0.1-0.5 ml/kg equivalent to 0.25-1.25 mg/kg. Children aged 5 years or older have received bupivacaine 5 mg/ml at a dose of 1.25-2 mg/kg.

For penile blocks, bupivacaine 5 mg/ml has been used at total doses of 0.2-0.5 ml/kg equivalent to 1-2.5 mg/kg.

The safety and efficacy of Bupivacaine Baxter in children <1 year of age have not been established. Only limited data are available.

Safety and efficacy of intermittent epidural bolus injection or continuous infusion have not been established. Only limited data is available.

4.3 Contraindications

- Hypersensitivity to the active substance, local anesthetic agents of the amide type or to any of the excipients listed in section 6.1.
- Intravenous regional anaesthesia (Bier's block)
- Not to be used for epidural anasthesia;
    - In patients with severe hypotension as in cardiogenic or hypovolemic shock
    - In presence of disease in the central nervous system, e.g. meningitis, poliomyelitis, tumores, (suspected) increased intracranial pressure, intracranial bleedings

- In presence of disease in columna vertebralis (e.g. spondylitis, tuberculosis, tumores, recent traumas), spinal stenosis
- Septikaemia
- Pernicious anaemia with subacute combined degeneration of medulla spinalis
- Pyogene infection at or around the place of injection
- Cardiogenic shock, hypovolaemic shock, cardiac insufficiency
- In presence of coagulation disturbances or active anticoagulant treatment (with the exception of low dose heparin).

4.4 Special warnings and precautions for use

Adequate resuscitation equipment should be available whenever local or general anaesthesia is administered. Before any major nerve block is attempted, intravenous access for resuscitation purposes should be established.

There have been reports of cardiac arrest during the use of bupivacaine for epidural anaesthesia or peripheral nerve blockade where resuscitative efforts have been difficult, and were required to be prolonged before the patient responded. However, in some instances resuscitation has proven impossible despite apparently adequate preparation and appropriate management.

Major peripheral nerve blocks may require the administration of a large volume of local anaesthetic in areas of high vascularity, often close to large vessels where there is an increased risk of intravascular injection and/or systemic absorption. This may lead to high plasma concentrations.
Like all local anaesthetic medicinal products, bupivacaine may cause acute toxicity effects on the central nervous and cardiovascular systems if utilised for local anaesthetic procedures resulting in high blood concentrations of the medicinal product. This is especially the case after unintentional intravascular administration.

Certain anaesthesia techniques are associated with serious adverse events:

- Epidural anaesthesia can cause cardiovascular depression especially in hypovolaemic patients. Local anaesthetics should be used with caution for epidural anaesthesia in patients with impaired cardiovascular function.
- Retrobulbar injections may very rarely reach the cranial subarachnoid space causing serious/severe reactions, including temporary blindness, cardiovascular collapse, apnoea, convulsions. These symptoms need immediate treatment.
- Retro- and peribulbar injections of local anaesthetics carry a certain risk of persistent ocular muscle dysfunction. The primary causes include trauma and/or local toxic effects on muscles and/or nerves.
- Unintentional intravascular injections into the head and neck regions may cause cerebral symptoms even at low doses.
- Paracervical block may sometimes cause bradycardia/tachycardia in foetus and the foetal heart rate should be closely monitored.

The extent of these tissue damages depends on the trauma size, the concentration of local anaesthetics and for how long the tissue been exposed to local anaesthetics. For this reason lowest effective dose must be used.

Local anaesthetics should be used with caution in patients suffering from AV-block II or III since it may depress the myocardial conductional system. Elderly patients with severe liver disease, significantly impaired kidney function or generally impaired condition also need special attention.

Patients treated with anti-arrhythmic medicinal products class III (e.g. amiodarone) should be under close surveillance and ECG monitoring, since cardiac effects of bupivacaine and anti-arrythmics may be additive.

Epidural anaesthesia with any local anaesthetic can cause hypotension and bradycardia which should be anticipated and appropriate precautions taken. These may include pre-loading the circulation with crystalloid or colloid solution. If hypotension develops it should be treated immediately with a vasopressor such as ephedrine 5-10 mg intravenously which is repeated as necessary.

There have been post-marketing reports on chondrolysis in patients treated post-operatively with local anaesthetics via continuous intraarticular infusion. The majority of the reported cases involve chondrolysis in the shoulder joint. Due to several contributing factors it has not been possible to establish a causal relationship. There is also inconsistency in the scientific literature regarding the mechanism of action. Continuous intraarticular infusion is not an approved indication for Bupivacaine Baxter.

This medicinal product contains 3,15 mg sodium per ml, equivalent to 0,16% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric population

Safety and efficacy of Bupivacaine Baxter in children aged <1 year has not been established. Only limited data are available.

The use of bupivacaine for intra-articular block in children 1 to 12 years of age has not been documented.
The use of bupivacaine for major nerve block in children 1 to 12 years of age has not been documented.

For epidural anaesthesia children should be given incremental doses commensurate with their age and weight as especially epidural anaesthesia at a thoracic level may result in severe hypotension and respiratory impairment.

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 class IB anti-arrhythmics since the toxic effects are additive.

Specific interaction studies with bupivacaine and other local anaesthetics or anti-arrhythmic medicinal product class III (e.g. amiodarone) have not been performed, but caution should be advised, (see also section 4.4).

4.6 Fertility, pregnancy and lactation

Fertility
There is no data on the influence of bupivacaine on fertility.

Pregnancy
Can be used during pregnancy. A large amount of pregnant women and women of childbearing age is assumed to have been treated with bupivacaine. There have been no reports of disturbancies of reproduction, e.g. no increased frequency of malformation (see also section 5.3 Preclinical safety data). Paracervical block increases the risk for foetal bradycardia/tachycardia and the foetal heart rate should therefore be closely monitored (see also section 5.2 Pharmacokinetics).

Breastfeeding
Bupivacaine enters the mother's milk, but in such small quantities that there is no risk of affecting the child at therapeutic dose levels.

4.7 Effects on ability to drive and use machines

Depending on the technique of anaesthesia and dose, bupivacaine may have a temporary effect on motor function and coordination, which may affect the ability to drive and use machines. It should be borne in mind that dizziness and seizures may occur.

4.8 Undesirable effects

Side effects caused by the drug itself can be difficult to distinguish from the physiological effects of the nerve block (e.g. hypotension, bradycardia), side effects caused by needling directly (e.g. nerve damage) or indirectly (e.g. epidural abscess).

Neurological damage is a rare but well known side effect of regional anaesthesia especially in epidural and spinal anaesthesia.

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

Adverse reactions are presented according to the MedDRA system organ classes and MedDRA frequency convention.

System organ class	**Frequency**	**Symptoms**
Immune system disorders	Rare (≥1/10 000, < 1/1000)	Allergic reactions, anaphylactic reactions/shock
Nervous system disorders	Common (≥1/100, < 1/10)	Paraesthesia, dizziness
	Uncommon (≥1/1000, < 1/100)	Signs and symptoms of CNS toxicity (convulsions, circumoral paresthesia, numbness of the tongue, hyperacusis, blurred vision, unconsciousness, tremor, light headedness, tinnitus, dysarthria).
	Rare (≥1/10 000, < 1/1000)	Neuropathy, periphery nerve injury, arachnoiditis, palsy, paraplegia
Eye disorders	Rare (≥1/10 000, < 1/1000)	Diplopia
Cardiac disorders	Common (≥1/100, < 1/10)	Bradycardia
	Rare (≥1/10 000, < 1/1000)	Cardiac arrest, cardiac arrhythmia
Vascular disorders	Very common (≥1/10)	Hypotension
	Common (≥1/100, < 1/10)	Hypertension
Respiratory, thoracic and mediastinal disorders	Rare (≥1/10 000, < 1/1000)	Respiratory depression
Gastrointestinal disorders	Very common (≥1/10)	Nausea
	Common (≥1/100, < 1/10)	Vomiting
Hepatobiliary disorders	Not known (cannot be estimated from the available data)	Hepatic dysfunction/increase of SGOT and SGPT*
Renal and urinary disorders	Common (≥1/100, < 1/10)	Urinary retention

* Hepatic dysfunction, with reversible increases of SGOT, SGPT, alkaline phosphates and bilirubin, has been observed following repeated injections or long-term infusions of bupivacaine. If signs of hepatic dysfunction are observed during treatment with bupivacaine, the medicinal product should be discontinued.

Paediatric population

Adverse drug reactions in children are similar to those in adults, however, in children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during 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

Symptoms:
Systemic toxic reactions primarily involve the central nervous system (CNS) and the cardiovascular system. Such reactions are caused by high blood concentrations of a local anaesthetic, which may appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularised areas (see section 4.4).

CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the medicinal product, both quantitatively and qualitatively.

Accidental intravascular injections of local anaesthetics may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, systemic toxicity appears later (15-60 minutes after injection) due to the slower increase in local anaesthetic blood concentration.

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are usually light-headedness, circumoral paraesthesia, numbness of the tongue, hyperacusis, tinnitus and visual disturbances. Dysarthria, muscular twitching or tremors are more serious and precede the onset of generalised convulsions. These signs must not be mistaken for neurotic behaviour. Unconsciousness and grand mal convulsions may follow, which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with respiration and possible loss of functional airways. In severe cases apnoea may occur. Acidosis extend the toxic effects of local anaesthetics.

Recovery is due to redistribution of the local anaesthetic medicinal product from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the medicinal product have been injected.

Cardiovascular system toxicity may be seen in severe cases and is generally preceded by signs of toxicity in the central nervous system. In patients under heavy sedation or receiving a general anaesthetic, prodromal CNS symptoms may be absent. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics, but in rare cases cardiac arrest has occurred without prodromal CNS effects. Cardiovascular toxic effects are often related to depression of heart and myocardial conductional system leading to decreased cardiac output, hypotension, AV block, bradycardia, and occasionally ventricular arrhythmias including ventricular tachycardia, ventricular fibrillation and cardiac arrest. After a rapid intravenous bolus injection the achieved bupivacaine blood concentration in the coronary vessels could be as high that the circulatory effects appear alone or before the effects on the CNS. With this mechanism myocardial depression could appear even as a first symptom of intoxication.

In children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during general anaesthesia.

Treatment

In case of total spinal block, adequate ventilation needs to be secured (free airways, oxygen, if required intubation and controlled breathing). In cases of hypotension / bradycardia a vasopressor is given, preferably with inotropic effect.

When there are signs of acute systemic toxicity administration of local anaesthetics should immediately be discontinued. Treatment to maintain good ventilation, oxygenation and circulation should be given.

Oxygen is always given. If required intubation and controlled breathing (if necessary with hyperventilation). For convulsions diazepam is given. In bradycardia atropine is given.

If circulatory failure occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressors, inotropes and / or lipid emulsions should be considered. Give i.v. fluids, dobutamine and if necessary norepinephrine. The dose should be adjusted to the clinical situation and according to current

guidelines. Ephedrine can also be tried. Should cardiac arrest occur a successful outcome may require prolonged resuscitative efforts.
Treat any acidosis. Children should be given doses commensurate with their age and body weight in the treatment of systemic toxicity.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Local anaesthetics, ATC code: N01BB01

Bupivacaine Baxter contains bupivacaine which is an amide local anaesthetic with a prolonged duration. Bupivacaine blocks conduction of impulses in nerve fibres via inhibition of sodium ion transportation through neural membranes. Similar effects can be seen in excitatory membranes in the brain and heart muscle.

The most prominent property of bupivacaine is the prolonged duration and the difference in duration time is relatively small comparing bupivacaine with and without ephinephrine. Bupivacaine is suitable for continuous epidural block. Lower concentrations give less effect on motor-nerve fibres and shorter duration and could be useful in longer pain management for example at delivery or post-operatively.

5.2 Pharmacokinetic properties

The absorption rate of bupivacaine depends upon the dose, the route of administration and the vascularity of the injection site. Intercostal block gives the highest plasma concentration (4 mg/l following a dose of 400 mg) depending on a rapid absorption whilst subcutaneous injection in abdomen gives the lowest concentrations in plasma. In children a rapid absorption is seen resulting in a high plasma concentration in caudal block (1-1.5 mg/l following a dose of 3 mg/kg).

Bupivacaine shows complete and biphasic absorption from the epidural space with half-lives in the order of 7 min and 6 h respectively. The slow absorption is rate-limiting in the elimination of bupivacaine, which explains why the apparent half-life after epidural administration is longer than that after intravenous administration.

Bupivacaine has a volume of distribution at steady state of 73 l, an intermediate hepatic extraction ratio of 0.40, a total plasma clearance of 0.58 l/min and a terminal half-life of 2.7 h. Half life during elimination in newborns is up to 8 hours longer than in adults. The half life in children above 3 months of age corresponds to the half life in adults.

In children the pharmacokinetics are similar to that in adults.

It is mainly bound to alpha-l-acid glycoprotein with plasma binding of 96 %. After major surgery an increase in total plasma concentration of bupivacaine has been observed. This is related to a postoperative increase in alpha 1-acid glycoprotein. The unbound, i.e. pharmacologically active, concentration is similar before and after surgery. This explains why plasma concentrations above toxic levels may be well tolerated.

Bupivacaine is extensively metabolised in the liver, predominately by aromatic hydroxylation to 4-hydroxy-bupivacaine and N-dealkylation to PPX, both mediated by cytochrome P450 3A4. Clearance of bupivacaine is therefore dependent on the hepatic perfusion and the activity of metabolizing enzymes.

Bupivacaine crosses the placenta and the unbound concentration of bupivacaine will be the same in mother and foetus. The degree of plasma protein binding in the foetus is less than in the mother, which results in lower total plasma concentrations in the foetus.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Bupivacaine may precipitate if diluted with alkaline solutions and should not be diluted or co-administered with sodium bicarbonate injections. This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

After first opening: to be used immediately and unused solution to discard.

6.4 Special precautions for storage

Do not refrigerate or freeze.

6.5 Nature and contents of container

10 ml type I clear glass vial with bromobutyl rubber closure
20 ml type I clear glass vial with bromobutyl rubber closure

Pack sizes:
5 and 10 X 10 ml Solution for Injection
1, 5 and 10 X 20 ml Solution for Injection

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.
The solution should be inspected visually prior to use.
Only clear solutions practically free from particles should be used.

Any unused solution should be discarded.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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

<Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

2021-07-14

<Detailed information on this medicinal product is available on the website of {name of Member State Agency}>