Baxter

Baxter Pharmaceuticals India Private Limited

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Quality of Paper/Board : Super Sun Shine	**Size of Artwork (In mm) : 400x175**
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Barcode Information:

Barcode Scan Report:

Packing: 20ml Tub. vial	**Plant Location : Injectable**
Country: Israel	**Language : English**
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Date: 31/03/21

Bupivacaine Injection BP
Bupivacaine Baxter 5 mg/ml

1 NAME OF THE MEDICINAL PRODUCT
Bupivacaine Baxter 5 mg/ml
Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One ml solution contains 5 mg bupivacaine hydrochloride.
Excipient(s) with known effect: Sodium Chloride
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Long acting local anaesthetic.

4.2 Posology and method of administration

Bupivacaine Baxter 5 mg/ml should only be used by clinicians with experience of regional anaesthesia or under their supervision. The lowest possible dose for adequate anaesthesia should be used.

In order to prevent inadvertent intravascular injections, it is important that great caution be exercised. Careful aspiration before and during the injection of the total dose is recommended. The total dose must be injected slowly, 25-50 mg/min or in divided doses with continuous verbal contact being maintained with the patient and controls of heart rate. In epidural injection of high doses, a test dose of 3-5 ml Marcaine adrenaline is recommended. An inadvertent intravascular injection can cause e.g. a brief increase in heart rate and inadvertent intrathecal injection can produce signs of spinal block. If toxic symptoms occur, the injection must be discontinued immediately.

The doses given below are guides, and the dosage should be adjusted according to the extent of the block and the patient's general condition.

For *infiltration anaesthesia* Bupivacaine Baxter 5 mg/ml 5-30 ml (25-150 mg bupivacaine hydrochloride) should be given.

For *diagnostic and therapeutic blocks* Bupivacaine Baxter 5 mg/ml 0.5-20 ml (2.5-100 mg bupivacaine hydrochloride), for example for trigeminal block 0.5-2.5 ml (2.5-12.5 mg) and for stellatum block 5-10 ml (25-50 mg) should be given.

For *intercostal block* Bupivacaine Baxter 5 mg/ml 2-3 ml (10-15 mg bupivacaine hydrochloride) per nerve up to a total of 10 nerves should be given.

For *larger blocks* (for example epidural, sacral and brachial plexus anaesthesia): Bupivacaine Baxter 5 mg/ml 15-30 ml (75-150 mg bupivacaine hydrochloride).

For *obstetric anaesthesia* (for example epidural anaesthesia and caudal anaesthesia for vaginal delivery and vacuum extraction) Bupivacaine Baxter 5 mg/ml 6-10 ml (30-50 mg bupivacaine hydrochloride). The doses are initial doses, which if necessary may be repeated every two to three hours.
For *epidural block* (for caesarean section): Bupivacaine Baxter 5 mg/ml 15-30 ml (75-150 mg bupivacaine hydrochloride).

For *continuous epidural anaesthesia* in the form of intermittent bolus doses, initially Bupivacaine Baxter 5 mg/ml 10 ml (50 mg bupivacaine hydrochloride) should be given, thereafter Bupivacaine Baxter 5 mg/ml 3-8 ml (15-40 mg bupivacaine hydrochloride) every 4-6 hours depending on the desired number of anaesthetised segments and the patient's age.

For continuous epidural infusion (for example postoperative pain relief):

	Concentration	Volume	Dose
Lumbar epidural infusion:			
Bolus[1]	5 mg/ml	2.5-5 ml	12.5-25 mg
Infusion	5 mg/ml	2.5-3.75 ml/hour	12.5-18.75 mg[2]
Thoracic epidural infusion:		2.5-5 ml	12.5-25 mg
Bolus[1]	5 mg/ml	1.25-2.5 ml/hour	6.25-12.5 mg
Infusion	5 mg/ml		
Epidural infusion for vaginal delivery:			
Bolus[1]	5 mg/ml	3-5 ml	15-25 mg
Infusion	5 mg/ml	1-2.5 ml/hour	5-12.5 mg

1) If an adequate bolus dose was *not* given in the previous hour.
2) The maximum recommended dose per day should not be exceeded (see below).

Account must be taken of the dose given intra-operatively.

In cases of combination with an opioid the dose of bupivacaine may be reduced.
- Throughout the time that the infusion is being given patients must be observed at regular intervals with regard to blood pressure, heart rate and possible toxic symptoms. If signs of a toxic effect are observed the infusion must be stopped immediately.

For children under 12 years the following dose is recommended:
Caudal block: Bupivacaine Baxter 5 mg/ml 0.25 ml/kg bodyweight up to 10 ml.

Maximum recommended doses
The maximum recommended dose on one and the same occasion is calculated on the basis of 2 mg/kg body weight, and for adults is a maximum of 150 mg within a four-hour period.
Bupivacaine Baxter 5 mg/ml: 30 ml (150 mg bupivacaine hydrochloride)
The maximum recommended dose during a 24-hour period is 400 mg. The total dose must be corrected on the basis of the patient's age, constitution and other relevant circumstances.

4.3 Contraindications
Hypersensitivity to the active substance, amide-type local anaesthetic agents or to any of the excipients.

Bupivacaine should not be used for intravenous regional anaesthesia (Bier's block). Bupivacaine should not be used for epidural anaesthesia in patients with pronounced hypotension such as in cardiogenic and hypovolaemic shock.

4.4 Special warnings and precautions for use
Regional or local anaesthetic procedures, except those of the most trivial in nature, should always be carried out in close proximity to resuscitation equipment. Before any major block, an intravenous cannula should be inserted before the local anaesthetic drug is injected.

There have been reports of cardiac arrest or death with the use of bupivacaine for epidural anaesthesia or peripheral nerve block. In certain cases, resuscitation has been difficult or impossible despite appropriate treatment.

Extensive peripheral nerve blocks can entail large volumes of local anaesthetics being administered to highly vascularised areas, often in close proximity to large blood vessels. In these cases, there is an increased risk of intravascular injection and/or systemic absorption, which can lead to high plasma concentrations.

Like all local anaesthetic agents, bupivacaine may cause acute toxic effects on the central nervous system and cardiovascular system when its use leads to high blood concentrations. This applies particularly after accidental intravascular administration or administration into highly vascularised areas.
Some regional anaesthesia techniques may be associated with serious adverse effects, as indicated below:
- Epidural anaesthesia can cause cardiovascular depression, particularly in cases of concomitant hypovolaemia. Therefore, caution should be exercised in patients with impaired cardiovascular function.
- In rare cases, retrobulbar injections may reach the cranial subarachnoid space and cause e.g. temporary blindness, cardiovascular collapse, apnoea and convulsions. These symptoms must be treated immediately.
- Retrobulbar and peribulbar injections with local anaesthetic agents involve some risk of persistent ocular muscle dysfunction. The main causes are traumatic nerve damage and/or local toxic effects on muscles and/or nerves from injected local anaesthetic.

The extent of this tissue damage depends on the degree of trauma, concentration of the local anaesthetic and how long the tissue has been exposed to the local anaesthetic. For this reason, the lowest effective dose should be chosen. Accidental intravascular injections in the head and neck area can cause cerebral symptoms even at low doses.
- Paracervical block can sometimes cause bradycardia/tachycardia in the foetus, and foetal heart rate should be carefully monitored.

Caution should be exercised in patients with grade II or III AV block since local anaesthetic agents can decrease the conduction capacity of the myocardium. The elderly and patients with severe hepatic disease, severely impaired renal function, patients in late stages of pregnancy or whose general condition is impaired also require special attention.

Patients being treated with class III antiarrhythmic agents (e.g. amiodarone) should be closely monitored and ECG monitoring considered since the cardiac effects of bupivacaine and class III antiarrhythmic agents may be additive.

Epidural anaesthesia may lead to hypotension and bradycardia. The risk of such effects can be reduced, e.g., by injecting a vasopressor. Hypotension should be treated promptly with a sympathomimetic intravenously, repeated as necessary.

There have been post-marketing reports of chondrolysis in patients receiving postoperative intra-articular continuous infusion of local anaesthetics. The majority of reported cases of chondrolysis have involved the shoulder joint. Due to multiple contributing factors and inconsistency in the scientific literature regarding mechanism of action, causality has not been established. Intra-articular continuous infusion is not an approved indication for Bupivacaine Baxter 5 mg/ml.
Paediatric population

The safety and efficacy of Bupivacaine Baxter 5 mg/ml in children aged < 1 year has not been established. Only limited data are available.

Use of bupivacaine for intra-articular block in children aged 1 to 12 years has not been documented.

Use of bupivacaine for major nerve block in children aged 1 to 12 years has not been documented.

For epidural anaesthesia, children should be administered gradually increasing doses proportional to their age and weight, since thoracic epidural anaesthesia in particular can result in severe hypotonia and decreased respiratory function.

4.5 Interaction with other medicinal products and other forms of interaction
Bupivacaine should be used with caution with other local anaesthetic agents or class IB antiarrhythmic agents as the systemic toxic effects are additive.
Specific interaction studies have not been performed with bupivacaine and class III antiarrhythmic agents (e.g. amiodarone), but caution is recommended (see also section 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation
Pregnancy:
Paracervical block increases the risk of reactions such as bradycardia/tachycardia in the foetus; therefore foetal heart rate must be closely monitored.
See also section 5.2 Pharmacokinetic properties.

Breast-feeding:
Bupivacaine passes into breast milk, but the risk of an effect on the child seems unlikely at therapeutic doses.

4.7 Effects on ability to drive and use machines

Depending on the dose and method of administration, bupivacaine may have a transient effect on mobility and coordination.

4.8 Undesirable effects
Side effects caused by the medicinal product itself can be difficult to distinguish from the physiological effects of the nerve blockade (e.g. fall in blood pressure, bradycardia), events caused directly by the needle puncture (e.g. nerve damage) or caused indirectly by the needle puncture (e.g. epidural abscess).
Neurological damage is a rare but well-known consequence of regional anaesthesia, particularly in epidural and spinal anaesthesia.
For information about symptoms and treatment of acute systemic toxicity, see section 4.9 Overdose

Organ system	Frequency	Symptom
Immune system disorders	Rare (≥1/10,000, < 1/1,000)	Allergic reactions, anaphylactic shock
Nervous system disorders	Common (≥ 1/100, < 1/10)	Paraesthesia, dizziness
	Uncommon (≥ 1/1,000, < 1/100)	Symptoms of CNS toxicity (convulsions, circumoral paraesthesia, numbness of the tongue, hyperacusis, visual disturbances, loss of consciousness, tremor, light-headedness, tinnitus, dysarthria).
	Rare (≥ 10,000, <1/1000)	Neuropathy, peripheral nerve damage, arachnoiditis, paresis, paraplegia
Eye disorders	Rare (≥1/10,000, < 1/1,000)	Double vision
Cardiac disorders	Common (≥1/100, < 1/10)	Bradycardia
	Rare (≥1/10,000, < 1/1,000)	Cardiac arrest, cardiac arrhythmias
Vascular disorders	Very common (≥1/10)	Hypotension
	Common (≥1/100, < 1/10)	Hypertension

Respiratory, thoracic and mediastinal disorders	Rare (≥1/10,000, < 1/1,000)	Respiratory depression
Gastrointestinal disorders	Very common (≥1/10)	Nausea
	Common (≥1/100, < 1/10)	Vomiting
Renal and urinary disorders	Common (≥1/100, < 1/10)	Urinary retention

Paediatric population
Side effects in children are similar to those in adults, but early signs of local anaesthetic toxicity in children may be difficult to detect in cases where the blockade is given under sedation or general anaesthesia.

Reporting 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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose
Acute systemic toxicity:
Symptoms:
Systemic toxic reactions involve the central nervous system and the cardiovascular system. These reactions are caused by high concentrations of local anaesthetic in the blood, which can occur as a result of accidental intravascular injection, overdose or unusually rapid absorption from highly vascularised tissue (see also section 4.4 Special warnings and precautions for use).

CNS symptoms are similar for all amide local anaesthetics, while cardiac symptoms differ more between different drugs, both quantitatively and qualitatively.
Accidental intravascular injections of local anaesthetics can cause immediate systemic toxic reactions (within seconds to a few minutes). Signs of systemic toxicity in cases of overdose occur later (15-60 minutes after injection) due to a slower increase in concentrations of local anaesthetic in the blood.

CNS toxicity occurs gradually, with symptoms and reactions of escalating severity. The first symptoms are usually light-headedness, circumoral paraesthesia, numbness of the tongue, hyperacusis, tinnitus and visual disturbances. Difficulty in articulating, muscle twitching or tremor are more serious and precede generalised seizures. These signs must not be interpreted as neurotic behaviour. Unconsciousness and grand mal seizures may follow and may last from a few seconds to several minutes. Hypoxia and hypercapnia occur rapidly following convulsions due to increased muscular activity and inadequate respiration. In severe cases, respiratory arrest may occur. Acidosis increases the toxic effects of local anaesthetics.

Recovery is due to metabolism of the local anaesthetic agent and distribution away from the central nervous system. This takes place rapidly unless very large amounts of the drug have been injected.

Cardiovascular effects generally imply a more serious situation and are usually preceded by signs of CNS toxicity, which may, however, be masked by general anaesthesia or heavy sedation with drugs such as benzodiazepines or barbiturates. A fall in blood pressure, bradycardia, arrhythmia and even cardiac arrest can occur as a result of high systemic concentrations of local anaesthetics. Cardiovascular toxic effects are often related to depression of the conduction system of the heart and myocardium, leading to reduced cardiac output, hypotension, AV block, bradycardia and sometimes ventricular arrhythmias including ventricular tachycardia, ventricular fibrillation and cardiac arrest. These states are often preceded by signs of severe CNS toxicity, e.g. in the form of convulsions, but in rare cases cardiac arrest has occurred without prodromal CNS effects. After a very rapid intravenous bolus injection, such high blood concentrations of bupivacaine may be reached in the coronary vessels that an effect on the circulation occurs alone or before CNS effects. With this mechanism, myocardial depression can then occur even as a first symptom of intoxication.

As children often receive major blocks only after general anaesthesia has been started, extra alertness to early signs of intoxication is required in this group.

Treatment:
In the event of total spinal blockade, ensure adequate ventilation (clear airways, oxygen, if necessary intubation and controlled ventilation). In the event of a fall in blood pressure/bradycardia, administer a vasopressor, preferably with an inotropic effect.

If signs of acute systemic toxicity occur, the administration of local anaesthetic agents should be stopped immediately and CNS symptoms (convulsion, CNS depression) must promptly be treated with appropriate airway/respiratory support and the administration of anticonvulsant drugs.

If cardiovascular depression occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, inotropic agents and/or lipid emulsion should be considered. Children must be given doses proportional to their age and bodyweight when treating of systemic toxicity.

If circulatory arrest should occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

Should cardiac arrest occur, a successful outcome may require prolonged resuscitative efforts.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Local anaesthetics
ATC code: N01BB01
Bupivacaine Baxter 5 mg/ml contains bupivacaine, which is a long-acting amide local anaesthetic agent. Bupivacaine reversibly blocks impulse conduction in the nerve fibres by inhibiting the transport of sodium ions through the nerve membrane. Similar effects can also be seen on excitatory membranes in the brain and cardiac muscle.
The most characteristic property of bupivacaine is its long duration, and the difference in duration of bupivacaine with and without adrenaline is relatively small. Bupivacaine is suitable for continuous epidural block. Lower concentrations have less effect on motor nerve fibres and a shorter duration and may be appropriate for longer-term pain relief, e.g. in childbirth or postoperatively.

5.2 Pharmacokinetic properties
The rate of absorption is dependent on dose, route of administration and perfusion at the injection site. Intercostal block produces the highest plasma concentrations (4 mg/l after a dose of 400 mg) due to rapid absorption, while subcutaneous injection in the abdomen produces the lowest plasma concentrations. In children, rapid absorption and high plasma concentrations are seen in caudal block (approx. 1-1.5 mg/l after a dose of 3 mg/kg).

Bupivacaine displays complete and biphasic absorption from the epidural space with half-lives of approx. 7 minutes and 6 hours respectively. The slow absorption is rate limiting in the elimination of bupivacaine, which explains why the elimination half-life is longer after epidural administration than after intravenous administration.

Bupivacaine's steady state volume of distribution is 73 litres, the hepatic extraction ratio is 0.40, total plasma clearance is 0.58 l/min and the elimination half-life is 2.7 hours. The elimination half-life is up to 8 hours longer in neonates than in adults. The half-life in children over 3 months is equivalent to that in adults.

The pharmacokinetics in children are similar to those in adults.

Plasma protein binding is 96% and takes places predominantly to alpha-1-glycoprotein. After a major operation, levels of this protein may be elevated and produce a higher total plasma concentration of bupivacaine. However, the unbound concentration of bupivacaine remains the same. This explains why plasma concentrations above toxic levels can be well tolerated.

Bupivacaine is metabolised almost entirely in the liver, predominantly by aromatic hydroxylation to 4-hydroxybupivacaine and N-dealkylation to pipecolylxylidine, both of which are mediated by cytochrome P450 3A4. Clearance is thus dependent on hepatic blood flow and the activity of the metabolising enzyme.

Bupivacaine crosses the placenta and the concentration of unbound bupivacaine is the same in the mother and the foetus. However, the total plasma concentration is lower in the foetus, which has a lower degree of protein binding.

5.3 Preclinical safety data
There are no preclinical safety data of relevance to the safety evaluation other than what has already been included in the summary of product characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
1 ml solution for injection contains:
8 mg sodium chloride for injection, sodium hydroxide/hydrochloric acid (to adjust pH), water for injections to 1 ml.

6.2 Incompatibilities
Alkalisation can cause precipitation as bupivacaine is poorly soluble at pH above 6.5.

6.3 Shelf life

36 months

After first opening to be used immediately and unused solution to discard.
After dilution: Chemical and physical in use stability has been demonstrated for 36 hours at 25°C.
From a microbiological point of view the product should be used immediately.

6.4 Special precautions for storage
Store below 30ºC. Do not refrigerate or freeze.

6.5 Nature and contents of container
Glass Vial, 5 x 20 ml
Glass Vial, 10 x 20 ml
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Bupivacaine is compatible when admixed with 0.9% w/v sodium chloride injection, Ringer Lactate Solution and Sufentanil Citrate 50µg/ml.

7 MANUFACTURER

Baxter Pharmaceuticals India Private Limited
Vasana-Chacharwadi,
Ahmedabad-382 213, India.

8 MARKETING AUTHORISATION HOLDER

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9 REGISTRATION NUMBER

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