1. NAME OF THE MEDICINAL PRODUCT
Bupicain® 2.5 mg/mL and adrenaline 5 mcg/mL
solution for injection
Bupicain® 5 mg/mL and adrenaline 5 mcg/mL
solution for injection
ATC Code: N01BB51
bupivacaine hydrochloride
adrenaline tartrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bupicain® and adrenaline	**2.5 mg/mL + 5 mcg/mL**	**5 mg/mL + 5 mcg/mL**
1 mL contains:		
– Active ingredients: –		
bupivacaine hydrochloride	2.500 mg	5.000 mg
adrenaline tartrate, equal to adrenaline	0.005 mg	0.005 mg

3. PHARMACEUTICAL FORM
Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Bupicain® can be used in all types of peripheral anaesthesia:
- local infiltration;
- troncular;
- locoregional;
- epidural sacral;
- sympathetic block;
- spinal subarachnoidal.

Bupicain® is, therefore, indicated for all cases of general surgery, orthopedics, ophthalmology, otorhinolaryngology, stomatology, obstetrics-gynaecology and dermatology. It can be used either alone or combined with narcosis.

4.2 Posology and method of administration
Bupicain® is generally used in very low doses that can vary as recommended, from 2-3 mg to 100-150 mg, as roughly indicated in the table.

Type of anaesthesia	Concentration (mg/mL)	Dosage		Comments
		mL	mg	
Trigeminal block	2.5	1–5	2.5–12.5	
	5	0.5–4	2.5–20	
Axillary block	2.5	20–40	50–100	
	5	10–30	50–150	
Stellate ganglion block	2.5	10–20	25–50	
Intercostal block	2.5	4–8	10–20	The dose is for every
	5	3–5	15–25	intercostal space
Epidural	2.5	30–40	75–100	
	5	10–20	50–100	
Continuous epidural	2.5	It starts with 10 mL and then continues with 3–5–8 mL every 4–6		
	5	hours, depending on the segments to be anaesthetised and on the age of the patient		
Sacral	2.5	15–40	37.5–100	
	5	15–20	75–100	
Splanchnic block	2.5	10–40	25–100	
Sympathetic lumbar block	2.5	10–40	25–100	
Retrograde IV block	5	15–25	75–125	
Pelvic block	5	20–30	100–150	
Spinal subarachnoid block	5	4	20	
	10	2	20	

The maximum dosage for an adult and for each administration should not exceed 150 mg, which correspond to 30 mL of the solution at the concentration of 5 mg/mL and to 60 mL of the solution at the concentration of 2.5 mg/mL; in a broad sense, the safe dose that should not be exceeded both for adults and for children is 2 mg/kg for each administration. Prolonged antalgic therapy usually uses doses that vary from 0.25 to 1 mg/kg of body weight. Administration can be repeated 2–3 times in 24 hours.

4.3 Contraindications

Hypersensitivity to the components or closely chemically related substances. Ascertained or presumed pregnancy. As a result of its vasoconstrictor content, the product is generally contraindicated for cardiopaths, serious arteriopathies, hypertensive subjects, subjects presenting ischaemic manifestations of any type or essential migraine, nephropaths, hyperthyroid subjects and diabetics. Moreover, the product is absolutely contraindicated in paracervical block and in regional intravenous anaesthesia (Bier Block).

4.4 Special warnings and precautions for use

The product must be used with absolute caution in subjects during treatment with MAOIs or tricyclic antidepressants.

Immediate access to suitable equipment, drugs and staff for emergency treatment must be ensured because, rare cases of serious reactions, at times with a lethal outcome, have been reported after the use of local anaesthetics, even without a case history of individual hypersensitivity.
The anaesthetic with adrenaline contains sodium metabisulfite; this substance can cause allergy-like reactions and serious episodes of asthma in sensitive subjects and especially in asthmatics.
Caution: the vials do not contain antiseptic excipients. They must be used for only one administration. Any remaining product must be discarded.
The total posology must be adjusted to suit the patient's general conditions, age and important case history details. The specific weight of Bupicain® 2.5 mg/mL and 5 mg/mL with or without a vasoconstrictor is 1.006 at 20°C and 0.997 at 37°C. If infiltrations are administered for local anaesthesia in areas that lack the possibility of collateral circulation (fingers, root of penis, etc.), it is a good precaution to use the anaesthetic without a vasoconstrictor to avoid ischaemic necrosis. Prior to use, the doctor must ascertain the status of circulatory conditions of the subjects to be treated. Any overdose of anaesthetic must be avoided and two maximum doses of the same must never be administered without a minimum interval of 24 hours. It is, however, necessary, to use the lowest doses and concentrations that can allow to obtain the sought for effect. It is advisable to use an adequate test dose, possibly in combination with adrenaline, in order to promptly avoid accidental intravenous or intrathecal injection. The anaesthetic solution must be injected with caution in small doses about 10 seconds after preventive aspiration. Especially when highly vascularised areas have to be infiltrated, it is advisable to allow about 2 minutes to elapse before proceeding with the actual locoregional block. The patient must be closely supervised to immediately suspend administration at the first sign of alarm (e.g. sensory changes). To achieve moderate ischaemia, Bupicain® 5 mg/mL + adrenaline 1:200,000 can be used by diluting the anaesthetic in equal parts with the physiological solution. At the concentration of 1:400,000 the effect of adrenaline is sufficiently weakened to avoid vasospasms that are too intensive as long as the drug is not injected into the lumen of the vessel.

4.5 Interaction with other medicinal products and other forms of interaction
No known interactions with other medicines. But caution is required in subjects treated with MAOIs or tricyclic antidepressants (see special warnings).

4.6 Pregnancy and lactation
Do not use the drug in case of ascertained or suspected pregnancy.

4.7 Effects on ability to drive and use machines
At the recommended doses, the drug does not influence reactive capacity neither significantly nor for extensive periods of time.

4.8 Undesirable effects
Toxic and allergic reactions can occur both to the anaesthetic and to the vasoconstrictor. The former include events of central nervous stimulation with excitation, shivers, disorientation, dizziness, mydriasis, increased metabolic rate and body temperature and, for very high doses, trismus and seizures. If the medulla oblongata is involved, this entails the joint participation of cardiovascular, respiratory and vomiting centres with perspiration,

arrhythmias, hypertension, tachypnoea, bronchial dilation, nausea and vomiting. Peripheral effects can involve the cardiovascular system with bradycardia and vasodilation. Allergic reactions especially occur in hypersensitive subjects but several cases are reported with no individual hypersensitivity stated in the case history. Local manifestations include various skin rashes, hives and itching. General manifestations include bronchial spasm, laryngeal oedema until cardiorespiratory collapse caused by anaphylactic shock. The vasoconstrictor, for its action on the circulation, can cause various types of abnormal effects especially in subjects who are not normal from a cardiocirculatory standpoint: asthma, perspiration, laboured breathing, cardiac arrhythmias, hypertension (particularly serious in subjects who are already hypertensive and in hyperthyroid subjects), intense headache, photophobia, retrosternal and pharyngeal pain, vomiting.

4.9 Overdose

At the first sign of alarm, interrupt the administration, place the patient in a horizontal position and ensure patency of airways, administering oxygen in case of serious dyspnoea or providing artificial ventilation (Ambu balloon). The use of bulbar analeptics must be avoided to prevent the situation from worsening by increasing oxygen consumption. Seizures, if any, can be controlled by using intravenous Diazepam in a dose of 10–20 mg. Instead, barbiturates that can enhance bulbar depression are not recommended. Circulation can be supported with the intravenous administration of cortisone-based drugs in appropriate doses. Diluted solutions of alpha-beta stimulants with a vasoconstrictive action (mephentermine, metaraminol and others) or of atropine sulphate can be added. A targeted concentration of sodium bicarbonate can be used intravenously as an antacid.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Bupicain® is a long-acting amide-type, local anaesthetic. Experimentations conducted on the mouse, guinea pig and rabbit have proven the higher analgesic potency and duration of the action of bupivacaine, compared to other local anaesthetics. Anaesthesia induced by Bupicain® lasts for a period from 4 to 20 hours, depending on the conditions of use. At the end of the actual anaesthesia, the pain reduction has a long duration, which allows to considerably reduce the administration of analgesics during the subsequent 24 hours.

5.2 Pharmacokinetic properties

The hematic peak of bupivacaine depends on several factors: type of block, concentration of the solution, presence or absence of adrenaline. Used without the vasoconstrictor at doses of 125–150 mg, the maximum concentrations (0.64 µg/mL) in whole venous blood are obtained 15–30 minutes after the epidural and caudal block. Specimens collected simultaneously from arterial blood provided concentrations that are in average 20–40% higher. Bupivacaine is distributed in body fluids and tissues, and its plasma half-life is over 2 hours. Metabolised in the liver, bupivacaine is prevalently excreted by the kidneys, both as such and as the metabolite.

5.3 Preclinical safety data

Acute toxicity has been studied in the mouse, guinea pig and rabbit. The LD_{50} of bupivacaine is 7.8 mg/kg IV and 82 mg/kg SC in the mouse, while in the guinea pig it is 50 mg/kg IP. In the preparation with vasoconstrictor (adrenaline

1:200,000), LD_{50} is 2.1 mg/kg IV and 95 mg/kg SC in the mouse, while in the rabbit it is 50 mg/kg SC. Prolonged administration in the rat of 12 mg/kg SC and of 10 mg/kg SC of bupivacaine + adrenaline for 4 weeks did not cause pathological manifestations in the various organs nor did it cause weight loss. No significant difference was observed, compared to controls, in rats treated for 90 days with 10 mg/kg SC of bupivacaine. No maternal or foetal damage was observed in rats and rabbits treated during the entire gestation period with 15 mg/kg/day SC of bupivacaine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium chloride, sodium metabisulfite, water for injections.

6.2 Incompatibilities
Not known.

6.3 Shelf life
The shelf-life of the product with the package intact in all its presentations is 24 months.

6.4 Special precautions for storage
None.

6.5 Nature and contents of container
5-10 mL neutral glass ampoule.

7. MARKETING AUTHORISATION HOLDER
Monico spa
via Ponte di Pietra 7, Venice Mestre

8. MARKETING AUTHORISATION NUMBERS

Bupicain® 2.5 mg/mL and adrenaline 5 mcg/mL	box containing 10 ampules of 5 mL	MA No.: 032948 034
Bupicain® 2.5 mg/mL and adrenaline 5 mcg/mL	box containing 10 ampoules of 10 mL	MA No.: 032948 059
Bupicain® 5 mg/mL and adrenaline 5 mcg/mL	box containing 10 ampoules of 5 mL	MA No.: 032948 073
Bupicain® 5 mg/mL and adrenaline 5 mcg/mL	box containing 10 ampoules of 10 mL	MA No.: 032948 097

9. DATE OF FIRST AUTHORISATION
24/07/2000

10. DATE OF REVISION OF THE TEXT
24/07/2005