BUPIVACAINE AGUETTANT 2.5 mg/mL, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bupivacaine hydrochloride monohydrate..... 2.64 mg
Quantity equivalent to anhydrous bupivacaine hydrochloride..... 2.50 mg

For 1 ml.

Excipient: sodium.
For a full list of excipients, see section 6.1.

One vial of 5 ml contains 13.20 mg of bupivacaine hydrochloride monohydrate.
One vial of 10 ml contains 26.40 mg of bupivacaine hydrochloride monohydrate.
One vial of 20 ml contains 52.80 mg of bupivacaine hydrochloride monohydrate.

3. Pharmaceutical form.
Solution for injections.

4. Clinical characteristics.
4.1. Indications

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

4.2. Posology and method of administration.
Bupivacaine should only be used by or under the supervision of clinicians experienced in local and regional anaesthesia. All equipment and medication required for monitoring and emergency resuscitation must be immediately available. An intravenous cannula should be prepared in patients before the institution of peripheral or central block or the infiltration of high doses. Continuous ECG monitoring must be performed.

Bupivacaine hydrochloride is available with or without epinephrine (1/200,000) at concentrations of 2.5 mg/ml and 5 mg/ml. The form and concentration used vary with the indication and intended purpose (surgical anaesthesia or simple analgesia), age and possible associated pathologies of the patient. The use of epinephrine-containing forms extends the duration of action. The most concentrated forms provide a more consistent and intense motor block.

The lowest possible concentration of anaesthetic should be given at the lowest dose needed to provide effective anaesthesia.

Adults
The following recommended doses serve as a guideline for an average adult, defined as a young man weighing 70 kg. Whatever the type of anaesthesia, the dose of the initial injection must not exceed 150 mg, except for spinal anaesthesia, where the dose of the initial injection must not exceed 20 mg.

Subsequent injections: injection of repeated doses of bupivacaine may result in marked increase in plasma concentrations of the drug due to accumulation. Consequently, the following instructions must be followed carefully:
- the second injection must not be given until at least 1/3 of the half-life of bupivacaine has elapsed, i.e. 45 minutes;

- the dose used for the second injection should not be more than one third of the maximum authorised initial dose if reinjection is given after 45 minutes, or half the initial dose if reinjection is given after 90 minutes;
- from the third injection onwards: injection of one-third of the initial dose after half of one half-life (i.e. 75 minutes), or injection of half of the dose after one half-life (i.e. 150 minutes).

Dosage reduction should be considered in elderly subjects, particularly if repeat injections are to be given.

Table 1: Dosage regimens for initial administration in adults and children aged 12 years and over**

	Solution	**Usual dose*- Maximum dose (mg)**	**Volume (ml)**
Local parietal infiltration	2.5 mg/ml	A few mg-2 mg/kg	A few ml-50
Peripheral nerve blocks			
Intercostal nerve blocks	5 mg/ml	10-15 per nerve Maximum of 150 in total	2-3 per nerve
Plexus blocks	2.5 mg/ml	62.5-150	25-40
Truncal blocks	5 mg/ml	100-150	20-30
	2.5 mg/ml	12.5-50 depending on the nerve	5-20
	5 mg/ml	25-100 depending on the nerve	5-20
Thoracic epidural anaesthesia for surgical procedures	5 mg/ml	25-50	5-10
Lumbar epidural anaesthesia for surgical procedures including caesarean section	5 mg/ml	75-150	15-30
Continuous lumbar epidural infusion for analgesia (postoperative, obstetric, treatment of neoplastic pain, etc.)	2.5 mg/ml	12.5-18.5/hour max dose/24 hours: 400 mg	5-7.5/hour
Caudal anaesthesia for surgical procedures	5 mg/ml	75-150	15-30
Spinal anaesthesia	5 mg/ml	5-20	1-4

*including test dose
**40 kg

Paediatric patients 1 to 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.

Table 2: Dosage recommendations for children under 12 years*

	Conc. mg/ml	Volume ml/kg	Dose mg/kg	Onset min	Duration of effect hours
ACUTE PAIN MANAGEMENT (per 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 (eg, 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]	

[*] or 40 kg

[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 7.5-12.5mg 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 AGUETTANT 2.5 mg/ml, solution for injections in children above 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.

Method of administration
The following rules apply equally for central nerve blocks and peripheral nerve blocks. None of these rules can exclude all risk of accidents (particularly convulsive or cardiac accidents); nevertheless, they can reduce the frequency and severity of such accidents.

Careful aspiration is recommended before and during injection to prevent intravascular injection. In the absence of contraindications, a test dose of 3 to 5 ml (1 to 2 ml in children) of bupivacaine 2.5 mg/ml with adrenaline 1:200 000 is recommended. Inadvertent intravascular injection can be identified by a temporary increase in heart rate or a fall in systolic blood pressure in the minute following injection. Accidental intrathecal injection can be identified by signs of spinal block (paraesthesia of legs, reduced sensation in the buttocks in conscious patients).

The main dose should be injected slowly in incremental steps of approximately 5 ml while closely observing the patient's vital functions and maintaining verbal contact. If toxic symptoms occur (see "Overdose"), the injection should be stopped immediately.

Where the two techniques are used simultaneously (for example, femoral block and sciatic block), the precautions should be applied in similar fashion: the total dose, even if given in incremental steps, constitutes the dose that must be taken into consideration.
In the event of administration of a mixture of local anaesthetics, the toxic risk must take account of the total dose injected and the rule of cumulative toxicity of mixtures must be applied strictly.

Special cases of the central anesthesia
It is recommended to introduce the solution at a temperature of approximately 20°C, since introduction of the solution at a lower temperature can be painful.

During spinal anesthesia, it should be remembered that the distribution of anesthesia depends on several factors, including volume of injections and position of the patient before and during injection. The dose should be decreased for elderly and women in the later stages of pregnancy due the potential risk of excessive spinal blockade.

Do not reuse the vial after the first opening.

4.3. Contraindications.
- Known hypersensitivity to local anaesthetics of the amide type or any drug component;
- intravenous regional anaesthesia;
- paracervical nerve block in obstetrics;
- general contraindications specific to epidural and spinal anaesthesia;
- injection damage in the infected site.

Injection of adrenaline containing bupivacaine in areas of end arteries (e.g. penile block, Oberst block) may cause ischemic tissue necrosis.

Note: No specific contraindications were identified for paediatric patients.

4.4. Warnings.
Athletes will be informed of the fact that this medicinal product contains an active substance that can produce a positive reaction in anti-doping tests.

General precautions
An intravenous line should be installed in patients before administering peripheral or central nerve block or infiltration of large doses.

The use of bupivacaine requires ensuring that intravascular injection is not performed.

Toxic blood concentrations can be observed after an inadvertent intravascular injection, an overdose or rapid absorption in a highly vascularised area. They can be the cause of serious adverse reactions, in particular neurological and cardiac (see "Undesirable effects" and "Overdose"). As with all local anaesthetics, rules exist concerning the method of administration of bupivacaine, to minimise the occurrence of toxic concentrations (see heading 4.2). None of these rules totally eliminates a possible adverse event; nevertheless they allow decreasing their frequency and severity.

Bupivacaine should be used solely by or under the responsibility of doctors who are experienced in the techniques of local or regional anaesthesia. Equipment and medicinal products necessary for monitoring and emergency intensive care measures should be immediately available.
Intensive care equipment should necessarily include anticonvulsants (thiopental, benzodiazepines), vasopressor agents, atropine, equipment necessary to intubate and oxygenate a patient, and a defibrillator. Lastly, the equipment should include a cardiac ECG monitor and allow continuous monitoring of blood pressure.

Precautions related to the method of anaesthesia
Anaesthesia by infiltration: when the area to be anaesthetized is extensive or highly vascularized, a solution of bupivacaine with adrenaline will be used, in the absence of contra-indications.

In epidural and spinal anaesthesia, hypovolemic patients (whatever the origin of the hypovolemia) can develop sudden and severe arterial hypotension and bradycardia independently of the local anaesthetic used. Hypovolemia should therefore be prevented. Cases of hypotension then will be treated with vasopressor agents and/or vascular re-filling.

The occurrence of a haematoma should be sought during the post-anaesthetic period, after a peripheral nerve block or an infiltration administered in patients receiving anticoagulant therapy for curative or prophylactic purposes. For the same reasons, the patient receiving a treatment which can decrease platelet aggregation (e.g. aspirin, ticlopidine), with severe thrombocytopenia or more generally, major abnormalities of haemostasis will be monitored closely.

Some methods of regional anaesthesia of the head and neck require specific precautions for use.

An inadvertent intravascular injection, even if done with a low dose, can induce cerebral toxicity.

Retrobulbar and peribulbar injection: a breach in the subarachnoid space can produce toxic reactions such as temporary blindness, cardiovascular collapse, apnoea, or seizures. Furthermore, with this technique, there is a slight risk of prolonged ocular motor disorders which can result in a lesion and/or a local toxic effect on muscle or nerve (see "Undesirable effects").

Possibility of extension to cervical block in case of very prolonged Trendelenburg's position.

Precautions related to cardiac toxicity of bupivacaine
The instructions concerning its method of administration should be complied with, in particular to prevent any risk of too-high plasma concentrations, which could cause severe ventricular rhythm disturbances: torsades de pointes, and ventricular tachycardia which may result in ventricular fibrillation followed by asystole.

Patients presenting with disorders of ventricular conduction, i.e. widening of the QRS complex, should receive especially attentive monitoring.

Bupivacaine should be used with caution in patients with a long QT interval because it prolongs the actual refractory period.

Although at the recommended doses bupivacaine does not have any effect on atrioventricular conduction, because of possible slowing of heart rate in case of an accidental overdose, the ECG of patients with complete atrioventricular block who do not have a pacemaker and are receiving bupivacaine will be monitored attentively.

With bupivacaine and unlike the majority of local anaesthetics, signs of cardiac toxicity can occur at the same time as signs of neurotoxicity, in particular in children.

Other precautions in some population of patients

Impaired liver function: since bupivacaine is metabolized by the liver, doses should be limited in patients with severe hepatic impairment and possible repeat injection, for example for epidural anaesthesia should be monitored strictly in such subjects to prevent an overdose.

For the same reason, bupivacaine should be used with caution whenever a disorder (shock, heart failure) or a concomitant therapy (beta-blocker) carries the risk of decreasing hepatic blood flow.

The elderly: due to decreased clearance of bupivacaine observed in the elderly, it is necessary to be cautious in case of repeat injection to prevent acute toxicity by accumulation.

Hypoxia and hyperkalaemia enhance the risk of cardiac toxicity of bupivacaine and can require dosage adjustment. Acidosis enhances the unbound fraction of bupivacaine and consequently can increase its neurological and cardiac toxicity. Similarly, patients with severe renal impairment are at risk of enhanced toxicity of bupivacaine because of acidosis that it can produce.

This medicinal product contains 3.15 mg of sodium per ml. Take this into account in persons who are following a strict low-sodium diet.

Paediatric population
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.
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.

Failed spinal blockade
Failed spinal blockade is common with local anaesthetics and may involve problems with lumbar puncture; errors in the preparation and injection of solutions; inadequate spreading of drugs through cerebrospinal fluid; failure of drug action on nervous tissue; and difficulties related to patient management.

4.5. Interactions with other drugs and other forms of interaction.
Bupivacaine should be used with caution in patients receiving anti-arrhythmia agents which have a local anaesthetic activity such as lidocaine and aprindine, because the toxic effects are additive.

4.6. Pregnancy and lactation.
Pregnancy

Do not use in a paracervical nerve block in obstetrical anaesthesia because of the risk of uterine hypertonia with an impact on the neonate (hypoxia).
Animal studies have not demonstrated any teratogenic effect but have demonstrated foetal toxicity.
In clinical practice, currently no sufficiently relevant data exists to evaluate a possible malformative effect of bupivacaine when administered in the first trimester of pregnancy.
Consequently, as a precautionary measure, it is preferable not to use bupivacaine during the first trimester of pregnancy.
Nevertheless, to date, in obstetrical use of bupivacaïne in late-term pregnancy or for delivery, no particular foetal toxic effect has been reported.

Lactation
As with all local anaesthetic agents, bupivacaine is excreted in breast milk. However, considering the low quantities excreted in breast-milk, breast-feeding is possible after regional anaesthesia.

4.7. Effects on ability to drive and use machines.
This product can alter the reaction capacity in drivers or users of machines, therefore patients shall avoid these activities.

4.8. Undesirable effects.

Adverse reactions related to local anaesthetics are very rare in the absence of overdose, abnormally rapid systemic absorption or inadvertent intravascular injection; in such cases, they can be very serious, especially in cardiac and neurological terms (see section 4.9).
In the absence of abnormally high plasma concentrations, the profile of undesirable effects of bupivacaïne is similar to that of other amide type local anaesthetics with long duration of action.

The above-mentioned undesirable effects have been depicted below.

Very common (> 1/10):

- *Vascular disorders*: hypotension,
- *Gastrointestinal disorders*: nausea.

Common (> 1/100):

- *Nervous system disorders:* headache related to lumbar puncture, paraesthesia
- *Ear and labyrinth disorders*: vertigo
- *Cardiac disorders:* bradycardia, tachycardia
- *Gastrointestinal disorders*: vomiting
- *Renal and urinary disorders:* urine retention
- *General disorders and administration site conditions:* hyperthermia

Uncommon (> 1/1.000):

- *Nervous system disorders:* hypoesthesia

Rare (> 1/10.000):

- *Immune system disorders:* allergic reactions (anaphylaxis)
- *Eye disorders:* strabismus, diplopia

Adverse reactions caused by the drug administration may be difficult to distinguish from the physiological effects of the nerve block (e.g. decrease in blood pressure, bradycardia), events caused directly (e.g. spinal haematoma) or indirectly (e.g. meningitis, epidural abscess) by needle puncture or events associated to cerebrospinal leakage (e.g. postural puncture headache).

During spinal anesthesia, headaches more frequently retrieved in young patients, could be prevented with use of 25 gauges needles.

Additionally, the following neurological complications which could have slow, incomplete, or no recovery, may occur after epidural or spinal anesthesia:

- persistent radiculopathy;
- peripheral neuropathy;
- paraplegia (extremity paralysis);
- partial or complete cauda equine syndrome manifested as urinary retention, fecal and urinary incontinence, loss of perineal sensation and sexual function, persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities and loss of sphincter control all of which may have slow, incomplete, or no recovery;
- intracranial subdural hematoma.

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.

4.9. Overdose

Injection in the cerebrospinal fluid of overdose of bupivacaine may result in extension of block which can lead total spinal anaesthesia.

An overdose, an inadvertent intravascular injection, abnormally rapid systemic absorption or accumulation due to delayed elimination can produce excessive plasma concentrations of bupivacaine; this results in signs of acute toxicity, which can lead to very serious undesirable effects. Such toxic reactions concern the central nervous system and the cardiovascular system.

Generally with local anaesthetics, signs of neurotoxicity precede signs of cardiac toxicity; however, due to the specific profile of cardiac toxicity of bupivacaine and because of the relatively frequent combination use of a local anaesthesia with sedation or general anaesthesia, in particular in children, signs of cardiac toxicity can be observed at the same time (or before) as signs of neurotoxicity. Measured in the venous blood, total circulating concentrations of bupivacaine; at which the first signs of cardiac and neurological toxicity can occur are 1.6µg/ml.

These effects are as follows.

Central nervous system.

It corresponds to a dose-dependent reaction, consisting of signs and symptoms of increasing severity. Initially, symptoms are observed such as agitation, apprehension, logorrhoea, yawning, sensations of inebriation, perioral paresthesia, numbness of the tongue, tinnitus and hyperacusis. These signs of alarm should not be erroneously interpreted as neurotic behaviour. Visual disorders and muscular twitches or contractions are more serious signs which can precede the development of generalized seizures. Then successively loss of consciousness and tonic-clonic seizures can occur whose duration can range from a few seconds to several minutes. Hypoxia and hypercapnia quickly occur in case of seizures as a result of increased muscular activity as well as respiratory disorders. Apnoea can occur in severe cases.

Cardiovascular effects.

Bupivacaine has specific cardiac toxicity. Elevated plasma concentrations can induce serious disorders of ventricular rhythm such as torsades de pointes, and ventricular tachycardia leading to ventricular fibrillation and asystole by electromechanical dissociation. Excessive plasma

concentrations can also induce major bradycardia and disorders of atrioventricular conduction; in terms of haemodynamic status, a decrease in cardiac contractility with hypotension can also be observed. All of these disorders can lead to cardiac arrest.

Treatment
It is necessary to have immediately available medicinal products and equipment for intensive care measures.

If signs of acute systemic toxicity occur during injection of the local anaesthetic, the latter should be immediately stopped.

Ventilation with pure oxygen by mask should immediately be initiated; sometimes it is sufficient to produce cessation of seizures. It is also necessary to make certain that the airways are patent.
If seizures do not cease within 15-20 seconds, an anticonvulsant will be administered intravenously such as thiopental (1-4 mg/kg) or a benzodiazepine (0.1 mg/kg diazepam or 0.05 mg/kg of midazolam); succinylcholine will be administered to facilitate intubation in case of refractory seizures.
Circulatory failure will be treated with a bolus dose of 5-10 μg/kg of adrenaline, without exceeding this dose to avoid inducing tachycardia or ventricular fibrillation.
Disorders of ventricular rhythm will be treated with defibrillation.

Necessary measures will be taken to counteract respiratory and metabolic acidosis, and against hypoxia to avoid worsening of signs of toxicity.

Monitoring will be extended because of extensive tissue binding of bupivacaïne.

5. Pharmacological properties.
Pharmacodynamic properties.
LOCAL ANAESTHETIC (N01BB01: central nervous system)
Bupivacaine belongs to the amide-linked group of anaesthetics.

The anaesthetic activity of bupivacaine is characterised by:
- slow onset of anaesthesia,
- long duration of action (extended when using the epinephrine combination),
- achievement of an almost exclusively sensory nerve block with the 2.5 mg/ml combination, or a nerve block associated with motor block of variable intensity with the 5 mg/ml concentration.

During anaesthesia administered by infiltration, the mean duration of anaesthesia achieved with a solution containing no adrenaline is 200 minutes.
During epidural lower back anaesthesia, onset of anaesthetic effect is seen within 5 minutes, with complete spread being noted in 20 minutes and a duration of 200 minutes (0.25 % solution) to 300 minutes (0.5 % solution).
During peripheral blocks, the time to onset of anaesthesia is 15- 20 minutes and the duration of the effect varies widely according to various factors, ranging from 6 to 24 hours with anaesthesia of certain plexuses.

5.2. Pharmacokinetic properties.
Absorption
The absorption and diffusion of bupivacaine depend on a large number of parameters:
- type of injection,
- patient profile,
- concentration, total dose injected,
- physico-chemical characteristics of the anaesthetic: high lipid solubility (preferential binding to lipid-rich tissues: heart, lung, brain), pka 8.1, pH 7.4, 83% of the unbound fraction of the drug is in ionised form.

Distribution
Binding to plasma protein (preferentially alpha-1 glycoprotein) is very high and is of the order of 95% at the standard therapeutic doses.
The half-life of distribution in tissue is approximately 30 minutes while the volume of distribution is 72 litres.
Bupivacaine crosses the placental barrier: the foetal/maternal blood ratio is around 1:3.
Metabolism and excretion
Bupivacaine is largely metabolized in the liver through degradation by the mono-oxygenase system dependent on cytochrome P450. Practically all bupivacaine injected is eliminated in the form of its metabolites. The main metabolite is 2.6 pipecoloxylidine. None of the metabolites of bupivacaine is active or toxic at the plasma concentrations observed. Approximately 5 to 10% of the substance is eliminated in the active form in urine.
The apparent half-life of elimination is 2.5 to 3.5 hours.
Plasma concentrations
For epidural anaesthesia involving a total dose of 150 mg of bupivacaine, peak plasma concentration is achieved within 10 to 30 minutes, reaching approximately 1 µg/ml.
Following epidural anaesthesia for obstetric applications involving doses of 50 mg to 100 mg of bupivacaine, maternal plasma concentrations range from 0.4 to 0.8 µg/ml.
Following brachial plexus block using 150 mg of bupivacaine, peak plasma concentration is achieved within 15 to 20 minutes, reaching approximately 1.50 to 1.70 µg/ml.
The plasma concentration at which the initial signs of neurological and cardiac toxicity appear is 1.6 µg/ml.

Children
In children the pharmacokinetics is similar to that in adults.

PHARMACEUTICAL PARTICULARS

List of excipients
Sodium chloride, sodium hydroxide, water for injections.

Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other drugs.

Shelf life.
3 years.

Special precautions for storage.
No special precautions for storage.

Nature and contents of container.
5, 10 and 20 ml vial (glass); box of 1
5, 10 and 20 ml vial (glass); box of 10
5, 10 and 20 ml vial (glass); box of 25
Cap (chlorobutyl)

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