BUPIVACAINE AGUETTANT 5mg/mL, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bupivacaine hydrochloride monohydrate..... 21.11 mg
Quantity equivalent to anhydrous bupivacaine hydrochloride..... 20.00 mg

For 4 ml.

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

3. Pharmaceutical form.

Solution for injections (IR)

4. Clinical particulars.

4.1. Therapeutic indications.

Spinal anesthesia at surgical procedures and treatment, which require precisely this kind of anesthesia: surgical treatment of lower extremities, urological surgical procedures with the use of endoscopy or abdominal surgery, gynecological operations, Caesarian section, abdominal surgery below the umbilicus line, in adults and children of all ages.

4.2. Posology and method of administration.

Bupivacaine can be used exclusively by doctors, highly experienced in local and regional anesthesia. All medical devices, equipment and medicinal products, required for monitoring and urgent intensive care should be accessible at any time. Droppers should be applied to patients prior to peripheral or central nerve block or high dose infiltration. Permanent ECG-monitoring should be provided.

The lowest possible concentration of anaesthetic should be given at the lowest dose needed to provide effective anaesthesia. The recommended doses are given in the table below.

	Conventional dose	Volume
Adults and children above 12 years of age*	5-20 mg**	1-4 ml
Neonates, infants and children under 12 years of age* • < 5 kg • 5 kg – 15 kg • > 15 kg	 0.40 - 0,50 mg/kg 0.30 - 0,40 mg/kg 0.25 - 0,30 mg/kg	 0.08 - 0,1 ml/kg 0.06 - 0,08 ml/kg 0.05 - 0,06 ml/kg

* Or 40 kg

** Elderly patients: 5-10 mg

Intraspinal injection of bupivacaine solution under high pressure for spinal anesthesia is made at a time without any air bubbles.

The recommended doses, indicated in the table below, are considered to be the doses relating to middle-aged adult patients, who are treated as young patients weighing up to 70 kg.

The volume of injected solution can be decreased or increased according to the patient body type (constitution) and, in particular, dependent upon the required length/duration of sensory canals block at the level, sufficient for the planned procedure, as well as the required motor lock rate.

The injected cumulative dose should not exceed 20 mg.

Children

One of the differences between small children and adults is a relatively high CSF volume in infants and neonates, requiring a relatively larger dose/kg to produce the same level of block as compared to adults.

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.

When using spinal anaesthesia, it must be kept in mind that the extent of the anaesthesia depends on several factors, including the dose injected and the position of the patient before and during the injection. Given the potential risk of having a spinal block that is too widely spread, the dosage will be decreased in elderly patients and in situations where intra-abdominal pressure is elevated (end of pregnancy, ascites, obesity).

The patient position effects distribution of bupivacaine for spinal anesthesia in cerebrospinal fluid due to hyperbaric nature of the solution. Clavicular section block (sacral part) can be achieved by making an injection to the seated patient and maintaining this position for approximately 10 minutes. When injecting bupivacaine for spinal anesthesia to the side-lying patient, it may be distributed in cranial or caudal directions relative to vertebral angle. If the patient remains in Trendelenburg's position for a long time, there’s a substantial risk of block distribution towards the neck (see “Peculiarities of usage”).

Method of administration

The solution is recommended to be used at temperature of approximately 20^0C, as solution injection at lower temperatures may be rather painful.

It is necessary to follow the instructions stated below. None of these instructions can exclude all risks of accidents/complications (in particular, convulsive attacks or heart attacks); however, they can reduce the frequency and severity of such complications.

Intensive breathing is recommended prior to and during injection, in order to avoid intravascular injection.

The principal dose should be injected slowly, gradually, at the same time taking special care of the patient vital functions and keeping up the conversation with the patient. In case of toxic symptoms emergence, the injection should be stopped immediately.

In case of injecting the combination of local anesthetics, the toxic risk has to account for injected cumulative dose, and the instructions for cumulative toxicity of combined anesthetics must be strictly followed.

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;
- general contraindications specific to epidural and spinal anaesthesia;

4.4. Peculiarities of usage.

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

This medicinal product contains sodium. The sodium content is less than 1 mmol per ampoule, i.e. “sodium free”.

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.The medicinal product is not injected intravenously.

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.

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

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 levels, the adverse reaction profile of bupivacaine is similar to that of other long-acting amide-linked local anaesthetics.

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 Overdosing.

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.

Cardio-vascular toxicity

Bupivacaine has a specific carditoxicity. Increased plasma concentration may cause serious disorders of ventricular rate, such as torsade de pointes and ventricular tachycardia, leading to ventricular fibrillation, asystolia (cardiac arrest) or electromechanical dissociation (pulseless electrical activity). Excessive plasma concentration may also cause considerable bradycardia and disorder of atrioventricular conduction; from the point of view of hemodynamic state the decreased heart rate with hypotonia may also be observed.

All these disorders may 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.

5.1. Pharmacodynamic properties.

LOCAL ANAESTHETIC. (N01BB01: central nervous system)

Bupivacaine is a prolonged-action analgesic and relates to the medicinal products for local anesthesia of amide group.

Bupivacaine solution for spinal anaesthesia has a density of 1026 at 20°C and 1020 at 37°C.

Sensor block takes place in 5 minutes after the injected bupivacaine for spinal anesthesia was started and lasts for maximum 20 minutes.

Duration of sensor and motor blocks depends upon the patient's initial position and the product's injected dose. Thus, after injection of 3 ml to the seated patient for 2 minutes, duration of D10-D12 block is 2 – 2.5 hours.

Motor block is developed simultaneously with sensor block, relaxation of stomach muscles and lasts 1 hour and from 2 to 2.5 hours for lower extremities. It also depends upon the patient's initial position and the product's dose.

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 3.5 hours.

Plasma concentrations

After administration of spinal anaesthesia, and taking into account the low quantity administered, the concentrations in the blood are very low.

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.

6. Pharmaceutical particulars.

List of excipients

Glucose monohydrate, sodium hydroxide, water for injections.

Incompatibilities

NA

Shelf-life

3 years.

Special precautions for storage

No special precautions for storage.

Nature and contents of outer packaging

4 ml vial (glass); box of 5
4 ml vial (glass); box of 20

Special precautions for disposal and handling

N/A.

MARKETING AUTHORISATION HOLDER

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