SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bupivacaine Aguettant 5 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains
Bupivacaine hydrochloride monohydrate..... 5.28 mg
Quantity equivalent to anhydrous bupivacaine hydrochloride..... 5.00 mg

Each 20 ml vial contains 100 mg of bupivacaine (as hydrochloride anhydrous).

Excipient(s) with known effect: Sodium
For the full list of excipients, see section 6.1.

Each ml of solution for injection contains 3.15 mg equivalent to 0.14 mmol of sodium. Each 20 ml vial contains 63 mg equivalent to 2.7 mmol of sodium.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Long acting local anaesthetic.

4.2 Posology and method of administration

Bupivacaine Aguettant should only be used by physicians with experience of regional anaesthesia or under the supervision of such a physician. The lowest possible dose for adequate anaesthesia should be sought.

It is important to observe particular caution in order to prevent inadvertent intravascular injections. Thorough aspiration before and during injection of the main dose is recommended. The main dose should be injected slowly at 25-50 mg/minute or in divided doses, while keeping continuous verbal contact with the patient and monitoring the heart rate. In epidural injection, the administration of high doses, a test dose of 3-5 ml bupivacaine with adrenaline is recommended. An inadvertent intravascular injection can cause symptoms such as a transient increase in heart rate and an inadvertent intrathecal injection can cause signs of spinal block. The injection should be discontinued immediately if there are any toxic symptoms.

The following doses are guidelines; the dosage should be adjusted according to the scope of the block and the patient's overall health status.

In *infiltration anaesthesia*, administer Bupivacaine Aguettant 5 mg/ml, 5-30 ml (25-150 mg bupivacaine hydrochloride).

For *diagnostic and therapeutic blocks*: Bupivacaine Aguettant 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.

In *intercostal block*, administer Bupivacaine Aguettant 5 mg/ml, 2-3 ml (10-15 mg bupivacaine hydrochloride) per nerve, up to a total of ten nerves.

In *major blocks* (such as epidural, sacral and brachial plexus anaesthesia): Bupivacaine Aguettant 5 mg/ml, 15-30 ml (75-150 mg bupivacaine hydrochloride).
In *obstetric anaesthesia* (such as epidural or caudal anaesthesia for vaginal childbirth and vacuum aspiration): Bupivacaine Aguettant 5 mg/ml, 6-10 ml (30-50 mg bupivacaine hydrochloride). The doses given are initial doses, which may be repeated every two to three hours if required.

In *epidural block* (for caesarean section): Bupivacaine Aguettant 5 mg/ml, 15-30 ml (75-150 mg bupivacaine hydrochloride).

In *continuous epidural anaesthesia* in the form of intermittent bolus doses, give an initial dose of Bupivacaine Aguettant 5 mg/ml, 10 ml (50 mg bupivacaine hydrochloride) should be given initially, thereafter Bupivacaine Aguettant 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.

In con*tinuous epidural infusion* (such as postoperative analgesia):

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

1) If an adequate bolus dose has *not* been given during the preceding hour.
2) The highest recommended dose per 24 hours should not be exceeded (see below).

Consideration should also be given to the dose given intraoperatively.

The bupivacaine dose can be reduced when used concomitantly with an opioid.
The patient must be monitored regularly during the entire time the infusion is ongoing with regards to blood pressure, heart rate and any symptoms of toxicity. The infusion must be discontinued immediately if any signs of toxicity are observed.

For children under 12 years the following dose is recommended:

Caudal block: Bupivacaine Aguettant 5 mg/ml, 0.25 ml/kg body weight up to 10 ml.

Maximum recommended doses

The maximum recommended dose for administration at one and the same time is calculated using the figure of 2 mg/kg body weight. For adults this is a maximum of 150 mg within a four hour period.
Bupivacaine Aguettant 5 mg/ml: 30 ml (150 mg bupivacaine hydrochloride).
The maximum recommended dose per 24 hours is 400 mg. The total dose must be adjusted with reference to the patient's age, general health and other relevant factors.

4.3 Contraindications

Hypersensitivity to the active substance, amide-type local anaesthetics or to any of the excipients listed in section 6.1.

Bupivacaine should not be used in intravenous regional anaesthesia (IVRA or Bier's block).
Bupivacaine should not be used in epidural anaesthesia in patients with pronounced hypotension such as in cases of cardiogenic or hypovolemic shock.

4.4 Special warnings and precautions for use

Procedures using regional or local anaesthesia should always be performed in the vicinity of resuscitation equipment unless the procedure is very minor. An intravenous cannula should be inserted prior to large blocks, before the injection of the local anaesthetic.

Reports have been received of cardiac arrest or death following the use of bupivacaine in epidural anaesthesia or peripheral nerve block. In some cases, resuscitation was difficult or impossible despite adequate treatment.

Extensive peripheral nerve blocks can involve the administration of large volumes of local anaesthetics to highly vascularised areas, often in the vicinity of large blood vessels. In such cases there is a heightened risk of intravascular injection and/or systemic absorption, which can lead to high plasma concentrations.
Like all local anaesthetics, bupivacaine may cause acute toxic effects on the central nervous and cardiovascular systems if use results in high blood concentrations. This applies particularly after inadvertent intravascular administration or administration to highly vascularised areas.

Some regional anaesthesia techniques may be associated with severe adverse reactions as follows:

- Epidural anaesthesia may cause cardiovascular depression, particularly in the case of concomitant hypovolemia. Caution should therefore be observed in patients with impaired cardiovascular function.
- Retrobulbar injections can, in rare cases, 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 of local anaesthetic are associated with a certain risk of residual ocular muscle dysfunction. The primary causes are traumatic nerve injuries and/or local toxic effects on muscles and/or nerves due to injection of local

anaesthetic.
The scope of the tissue damage depends on the magnitude of the trauma, the concentration of local anaesthetic and the duration of exposure of the tissue to local anaesthetic. For this reason, the lowest possible effective dose should be used. Inadvertent intravascular injections in the head and neck regions can cause cerebral symptoms even at low doses.

- Paracervical block can sometimes cause bradycardia or tachycardia in the foetus; the foetal heart rhythm must be closely monitored.

Caution should be observed in patients with AV block II or III, as local anaesthetics may decrease myocardial transmittance. Particular attention should also be paid to the elderly and patients with severe hepatic disease or severe renal impairment, patients in the late stage of pregnancy or with poor general health.

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

Hepatic dysfunction, with reversible increases in aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase (ALP), and bilirubin, have been observed in rare cases following repeated bupivacaine injections or bupivacaine infusions of long duration. Immediate discontinuation of bupivacaine has led to rapid clinical improvement. If signs of hepatic dysfunction are observed during administration of bupivacaine, the medicinal product must be discontinued immediately. (See section 4.8).

Epidural anaesthesia can lead to hypotension and bradycardia. The risk of such effects can be reduced by e.g. injection of a vasopressor. Hypotension should be treated immediately with administration of an intravenous sympathomimetic and repeated if required.

There have been post-marketing reports of chondrolysis in patients receiving continuous postoperative intra-articular infusions of local anaesthetic. The majority of reported cases concerned chondrolysis in the shoulder joint. It has not been possible to establish a causal link due to several contributing factors as well inconsistencies in the scientific literature with regard to the mechanism of action. Continuous intra-articular infusion is not an approved indication for Bupivacaine Aguettant 5 mg/ml.

Paediatric population

The safety and efficacy of bupivacaine in children younger than one year of age have not been established. Only limited data are available.

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

The use of bupivacaine for major nerve blocks in children aged 1 to 12 years has not been documented.

In epidural anaesthesia, children should be given incrementally increasing doses in proportion to their age and weight, as epidural anaesthesia at the thoracic level in particular can result in severe hypotension and impaired respiration.

This medicinal product contains 63 mg sodium per 20 ml vial, equivalent to 3.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Bupivacaine should be used with caution in combination with other local anaesthetics or class IB antiarrhythmics, as the systemic toxic effects are additive.

No specific interaction studies have been carried out for bupivacaine and class III antiarrhythmics (e.g. amiodarone), but caution is recommended (see also section 4.4, Special warnings and precautions for use).

4.6 Pregnancy and lactation

Pregnancy:

As paracervical blockade increases the risk of reactions such as bradycardia and tachycardia in the foetus, close monitoring of the heart rate is required.

See also section 5.2, Pharmacokinetic properties.

Breastfeeding:

Bupivacaine is excreted into human milk but the risk of impact on the child is considered 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

Undesirable effects caused by the medicinal product itself may be difficult to distinguish from the physiological effects of nerve block (e.g. decrease in blood pressure, bradycardia), cases caused directly by the needle puncture (e.g. nerve damage), or cases caused indirectly by the needle puncture (e.g. epidural abscess).

Neurological injury is a rare but well-known consequential adverse effect of regional anaesthesia, particularly in epidural and spinal anaesthesia.

For information on the symptoms and treatment of acute systemic toxicity, refer to section 4.9, Overdose.

Organ system	**Frequency**	**Symptoms**
Immune system disorders	Rare (≥1/10,000, <1/1,000)	Allergic reactions, anaphylactic shock
Central and peripheral nervous system disorders	Common (≥1/100, <1/10)	Paraesthesia, dizziness

	Uncommon (≥1/1,000, <1/100)	Symptoms of CNS toxicity (convulsions, circumoral paraesthesia, tongue numbness, hyperacousis, vision disturbances, loss of consciousness, tremor, feeling of intoxication, tinnitus, dysarthria).
	Rare (≥1/10,000, <1/1,000)	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)	Urine retention
Hepatobiliary disorders	Not known (cannot be estimated from the available data)	Impaired hepatic function/increase in ASAT and ALAT*.

*Hepatic impairment, with reversible increases in ASAT, ALAT, ALP, and bilirubin, have been observed following repeated bupivacaine injections or bupivacaine infusions of long duration. If signs of hepatic impairment are observed during treatment with bupivacaine, the medicinal product must be discontinued immediately. (See section 4.4).

Paediatric population
Adverse reactions in children are similar to those in adults, but it may be difficult to detect early signs of local anaesthetic toxicity in children when blockade is given under sedation or general anaesthetic.

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.
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 include effects on the central nervous system and cardiovascular system. These reactions are caused by high blood concentrations of local anaesthetic, which may arise due to inadvertent intravascular injection, overdose or unusually rapid absorption from highly vascularised tissues (see also section 4.4, Special warnings and precautions for use).
CNS symptoms are similar for all amide-type local anaesthetics, however cardiac symptoms differ between different medicinal products, both quantitatively and qualitatively.

Inadvertent intravascular injections of local anaesthetics can cause immediate systemic toxic reactions (within seconds to a couple of minutes). Signs of systemic toxicity in the case of overdose occur later (15-60 minutes after injection) due to a slower increase in the blood concentration of the local anaesthetic.
CNS toxicity appears gradually, with symptoms and reactions of increasing severity. The initial symptoms are usually a feeling of intoxication, circumoral paraesthesia, tongue numbness, hyperacousis, tinnitus and visual disturbances. Articulation difficulties, muscle spasms or tremor are more severe symptoms and precede generalised convulsions. These symptoms should not be interpreted as neurotic behaviour. Unconsciousness and grand mal convulsions can follow the symptoms listed above, and may last from a few seconds to several minutes. Hypoxia and hypercapnia develop rapidly, with subsequent convulsions due to increased muscle activity and insufficient ventilation. Respiratory arrest may occur in severe cases. Acidosis intensifies the toxic effects of local anaesthetics.
Recovery is dependent on the metabolism of the local anaesthetic and on distribution away from the central nervous system. The process is rapid unless very large amounts of medicinal

product have been injected.
Cardiovascular effects usually indicate a more serious situation and are usually preceded by signs of CNS toxicity, however these may be masked by general anaesthesia or heavy sedation with drugs such as benzodiazepines or barbiturates. Blood pressure drops, bradycardia, arrhythmia and even cardiac arrest can occur as a result of high systemic concentrations of local anaesthetic. Cardiovascular toxic effects are often related to depression of transmission in the heart and myocardium which lead to decreased minute volume, hypotension, AV block, bradycardia and sometimes ventricular arrhythmias including ventricular tachycardia, ventricular fibrillation and cardiac arrest. These conditions are often preceded by signs of severe CNS toxicity such as convulsions, but in rare cases cardiac arrest has occurred in the absence of prodromal CNS effects. Following a very rapid intravenous bolus injection, the blood concentration of bupivacaine can be so high in the coronary vessels that circulatory effects arise, alone or preceding CNS effects. Myocardial depression can occur via this mechanism, potentially as the initial symptom of toxicity.

Extra attention must be paid to early signs of toxicity in paediatric patients, as children do not usually receive large blocks until after general anaesthesia has been initiated.

Treatment:
Adequate ventilation (free airways, oxygen, and intubation and controlled respiration if required) must be ensured in the case of total spinal blockade. In the case of a fall in blood pressure or bradycardia, administer a vasopressor, preferably with inotropic effect.

If signs of acute systemic toxicity appear, administration of the local anaesthetic must be immediately suspended and CNS symptoms (convulsions, CNS depression) treated immediately with optimal oxygen supply/ventilation support and the administration of anticonvulsants.

If circulatory arrest should occur (hypotension, bradycardia), appropriate treatment with IV fluids, vasopressors, inotropic agents and/or lipid emulsions should be considered. Children should be administered doses in proportion to their age and body weight when treating systemic toxicity.

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

Extended resuscitation may be warranted in the case of circulatory arrest.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Local anaesthetics

ATC code: N01BB01

Bupivacaine Aguettant 5 mg/ml contains bupivacaine, which is a long-acting amide-type local anaesthetic. Bupivacaine reversibly blocks impulse transmission in nerve fibres by inhibiting the transport of sodium ions over the nerve cell membrane. Similar effects can also be seen on excitatory membranes in the brain and cardiac muscle.

The most prominent characteristic of bupivacaine is the long duration of action; the difference in duration of action between bupivacaine with and without adrenaline is relatively small.
Bupivacaine is well suited to continuous epidural blockade. Lower concentrations have a lesser effect on motor nerve fibres and a shorter duration of action, and can be suitable for prolonged analgesia, such as in childbirth or postoperatively.

5.2 Pharmacokinetic properties

The absorption rate is dependent on the dose, route of administration and vascularisation of the injection site. Intercostal blocks lead to the highest plasma concentrations (4 mg/l following a dose of 400 mg) due to rapid absorption; subcutaneous abdominal injections lead to the lowest plasma concentrations. Rapid absorption and a high plasma concentration are seen in children following caudal block (approx. 1-1.5 mg/l following a dose of 3 mg/kg).

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

The distribution volume of bupivacaine at steady state is 73 litres; the hepatic extraction ratio is 0.40; total plasma clearance is 0.58 l/min; the elimination half life is 2.7 hours. The elimination half life in newborns is up to 8 hours longer than in an adult. The half life in children aged over 3 months is equivalent to that in adults.
The pharmacokinetics in children is similar to that in adults.

Plasma protein binding is 96% and primarily involves alpha-1-acid glycoprotein. There may be an elevated level of this protein following major surgery, giving a higher total plasma concentration of bupivacaine. The unbound concentration of bupivacaine will however remain unchanged. This explains why plasma concentrations that exceed the toxic level can be well tolerated.
Bupivacaine is almost entirely metabolised in the liver, primarily through aromatic hydroxylation to 4-hydroxy-bupivacaine and N-dealkylation to pipecoloxylidide, both of which are mediated by cytochrome P450 3A4. Clearance is therefore dependent on the hepatic blood flow and the activity of the metabolising enzyme.

Bupivacaine crosses the placenta and the concentration of unbound bupivacaine in the mother and foetus is equalised. However, the total plasma concentration will be lower in the foetus due to a lower degree of protein binding.

5.3 Preclinical safety data

There is no preclinical safety data of relevance to the safety assessment additional to that which has already been taken into consideration in the summary of product characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, sodium hydroxide (for pH adjustment), water for injections.

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
The preservative-free solution should be used immediately after opening the packaging.

6.4 Special precautions for storage

Store below 30ºC.

6.5 Nature and contents of container

Glass vial, 10 x 20 ml.

6.6 Special precautions for disposal and other handling

The product should be inspected visually for particles and discoloration prior to administration. Only clear colourless or slightly yellow solution free from particles or precipitates should be used.

7. MANUFACTURER

Delpharm Tours, Rue Paul Langevin, 37170 Chambray Les Tours, France.

8. MARKETING AUTHORISATION HOLDER

MBI Pharma Ltd, POB 5061

Kadima

9. REGISTRATION NUMBER

169-72-36306-00

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