ATROPINE AGUETTANT 0.1 MG/ML

1. NAME OF THE DRUG
Atropine Aguettant 0.1 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of solution for injection contains 0.1 mg atropine sulfate monohydrate, equivalent to 0.083 mg atropine.
Each 5 ml syringe contains 0.5 mg atropine sulfate monohydrate, equivalent to 0.415 mg atropine.
Excipient with known effect: sodium
Each ml of solution for injection contains 3.5 mg equivalent to 0.154 mmol of sodium.
Each 5 ml syringe contains 17.7 mg equivalent to 0.770 mmol of sodium.

For the full list of the excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection in pre-filled syringe.
pH 3.2-4.0.

4. CLINICAL INFORMATION

4.1 Therapeutic indications
Preanesthetic medication to decrease excessive salivation and secretions of the respiratory tract.
Treatment of sinus bradycardia, particularly if complicated by hypotension.
Antidote in poisoning by organophosphorus.

4.2 Posology and method of administration
Pre-anesthetic medication
Adults: The recommended dose is 0.3-0.6 mg by intravenous injection immediately before the anesthesia induction or by intramuscular injection 30-60 minutes before the induction.
Children: The recommended dose is 0.02 mg/kg (maximum dose 0.6 mg).

Treatment of sinus bradycardia
The recommended dose is between 0.3 and 1.0 mg intravenously.

Antidote in poisoning by organophosphorus *Adults*: The recommended dose is 2 mg (intramuscularly or intravenously, taking into account the poisoning severity) every 5-10 minutes, until the skin becomes red and dry, pupils dilate and tachycardia appears.
Children: The recommended dose is 0.02 mg/kg.

Method of administration

Atropin Aguettant 0.1mg/ml is not appropriate to deliver a dose of less than 0.5 ml.

Atropine Aguettant 0.1mg/ml is administered by intravenous injection or intramuscular injection. Other pharmaceutical forms/strengths may be more appropriate in the cases where a dose above 0.5 mg is required.

4.3 Contraindications
Hypersensitivity to the active ingredient or to any of the excipients listed in section 6.1.
Angle-closure glaucoma, esophageal reflux, pyloric stenosis, gastrointestinal obstruction, ulcerative colitis, prostatic hypertrophy, paralytic ileus, intestinal atony, myasthenia gravis (unless co-administered with anticholinesterase).

However, all these contraindications are irrelevant in potentially fatal emergency situations (such as bradyarrhythmia, poisoning).

4.4 Special warnings and precautions for use
The solution should be clear, colourless and free of visible particles.
The pre-filled syringe is intended for a single, uninterrupted administration and any unused residual solution should be discarded.
Atropine sulfate should be used with caution in children, the elderly and patients with Down syndrome.
Precautions should be taken in geriatric patients for whom you may need a dose adjustment due to a possible occurrence of adverse events related to the cardiovascular system and the central nervous system.

Use with caution in patients with ileostomy or colostomy; the occurrence of diarrhea may indicate an incomplete intestinal obstruction.
Use with caution in cases of:
- Hyperthyroidism
- Renal or hepatic insufficiency
- Coronary alterations, acute myocardial ischemia, acute myocardial infarction, tachycardia, tachyarrhythmia.
- Obstructive uropathies
- Chronic obstructive pulmonary disease, because the reduction of bronchial secretions may lead to the formation of bronchial caps
- Urinary retention
- Fever or when the ambient temperature is high.

Cases of atrioventricular paradoxical blockade or sinus arrest have been reported following administration of atropine in some patients after cardiac transplantation. The use of atropine for therapeutic or diagnostic procedures in patients undergoing heart transplantation should be undertaken with extreme caution.

Doses of atropine up to 1 mg slightly stimulate the central nervous system. Higher doses may induce mental disorders and central nervous system depression. Children and the elderly are particularly sensitive.

Care should be taken when using atropine in the presence of ischemia, as ischemia or infarction may be worsened.

This medicinal product contains sodium. Sodium level is lower than 1 mmol per syringe, i.e. ‘without sodium’.

4.5 Interaction with other medicinal products and other forms of interaction
<u>Contraindicated associations</u>
Derivatives of Belladonna: increase of the anticholinergic activity.
Halothane: attenuation of the depressor effect on heart rate.

Procainamide: increased vagal effects at atrioventricular level.
Methacholine: inhibition of the bronchoconstriction induced by methacholine inhalation.

Combinations to be taken into consideration
Other drugs with anticholinergic activity, such as tricyclic antidepressants, some anti-H1 antihistamines, antiparkinsonian drugs, disopyramide, mequitazine, phenothiazines, neuroleptic drugs, atropine antispasmodics, clozapine and quinidine, due to the risk of intensification of atropine adverse effects (urinary retention, constipation, dry mouth).

4.6 Fertility, pregnancy and lactation
Pregnancy
Data obtained from a limited number of exposed pregnancies indicate that atropine has no adverse effects on pregnancy or on the health of the fetus/newborn.
Animal studies do not indicate direct or indirect harmful effects of reproductive toxicity (see section 5.3).
Studies of the pharmacokinetics of atropine in mothers and fetuses in late stage pregnancies indicate that atropine rapidly crosses the placental barrier. Intravenous administration of atropine during pregnancy or at the end of pregnancy may cause tachycardia in the fetus and in the mother.
Atropine should not be used during pregnancy, unless clearly needed.

Lactation
Small amounts of atropine may pass into human breast milk. Newborns have a greater sensitivity to the anticholinergic effects of atropine. Atropine may inhibit milk production, particularly in case of repeated use. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from treatment, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. If you decide to continue breast-feeding during treatment, your child should be monitored for the presence of anticholinergic effects.

Fertility
No data is available on the effects of atropine sulfate on fertility in humans. Atropine sulfate has reduced the fertility of male rats, presumably as a result of the inhibitory effect on the transport of sperm and ejaculation.

4.7 Effects on ability to drive and use machines
Atropine affects your ability to drive or use machines.

4.8 Side effects
Below are the side effects of atropine organized according to the MedDRA system organ classification. There are insufficient data to determine the frequency of the single effects listed.

Endocrine disorders
Change in the levels of the growth hormone.

Metabolism and nutrition disorders
Porphyria, hyperthermia, hypothermia.

Nervous system disorders
Sedation, disorientation, dizziness, impaired short-term memory, psychosis, hallucinations (especially at higher doses), convulsions, headache.

Eye disorders
Diplopia, disturbances in accommodation, mydriasis, changes in intraocular pressure.

Cardiac disorders
Angina, arrhythmias, transient bradycardia (followed by tachycardia, palpitations and arrhythmias), atrioventricular block, hypertension, tachycardia.

Vascular disorders
Flushes.

Respiratory, thoracic and mediastinal disorders
Reduction of bronchial secretions.

Gastrointestinal disorders
Esophageal reflux, dry mouth with difficulty swallowing and talking, nausea, vomiting, feeling of swelling, inhibition of gastric secretion.

Skin subcutaneous tissue
Redness and dryness of the skin, hives, rush.
In case of intramuscular administration, a reduced activity of the sweat glands can be observed.

Renal and urinary disorders
Inhibition of the parasympathetic control of the urinary bladder, urinary retention.

General disorders and administration site conditions
Hypersensitivity reactions – Anaphylactic reactions.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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
Symptoms:
In case of an overdose of the drug, you may have the intensification of the side effects described. In particular, dryness of mucous membranes, dilated pupils, tachycardia, fever and skin rash are possible; neurological symptoms such as confusion, hallucinations, etc., that can persist for 48 hours or more, can also be observed. In some cases respiratory depression, coma, circulatory collapse and death can be observed.

Treatment:
At the first signs, in the case of respiratory depression, it is recommended to administer oxygen and, in the case of a persistence of seizures, if the circulatory conditions permit it, proceed with an intravenous administration of short-acting barbiturates (e.g. thiopental) or benzodiazepines (e.g. diazepam). Since atropine is excreted through the kidneys, an intravenous administration of fluids is recommended. In case of delirium and coma, the administration of physostigmine by a slow intravenous infusion at a dose range of 1 to 4 mg (0.5 to 1 mg in children) is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Belladonna alkaloids, tertiary amines.
ATC code: A03BA01
Atropine is an antimuscarinic alkaloid. It acts as an antagonist of peripheral muscarinic cholinergic receptors, which become insensitive to the action of acetylcholine that is released by the parasympathetic autonomic endings. This elective action explains the pharmacotherapeutic activity of the product.

5.2 Pharmacokinetic properties

Distribution
Atropine is rapidly distributed in the tissues after an intravenous administration (distribution volume of 3,297 L/kg in normal subjects). Atropine crosses the blood-brain barrier and has a half-life of 4 hours.

Metabolism and excretion
About half of a dose is metabolized and eliminated by the liver, while the remaining half is excreted unchanged in the urine. Atropine crosses the placenta and traces appear in breast milk.

5.3 Preclinical safety data

In preclinical studies, effects were observed only at exposures considered sufficiently in excess of the maximum human exposure, which indicates little clinical relevance.
Atropine sulfate has reduced fertility in male rats, presumably as a result of an inhibitory effect on the transport of sperm and ejaculation.

6. PHARMACEUTICAL INFORMATION

6.1 List of the excipients

Sodium chloride, concentrated hydrochloric acid, water for injections.

6.2 Incompatibility

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 product should be used immediately after opening. Any unused residual solution should be discarded.

6.4 Special precautions for storage.

Store below 30°C.

6.5 Nature and capacity of the container.

5 ml solution in a pre-filled syringe (polypropylene) without needle, individually packaged in a transparent blister, available in box of 10.

6.6 Special precautions for disposal and other handling

Instructions for use:

Be careful to strictly respect the protocol for the use of the syringe.

The pre-filled syringe is for single patient only. Discard syringe after use. DO NOT REUSE.

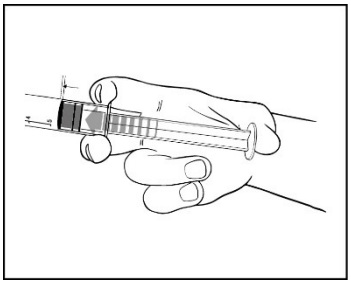
The content of un-opened and un-damaged blister is sterile, and must not be opened until used.

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

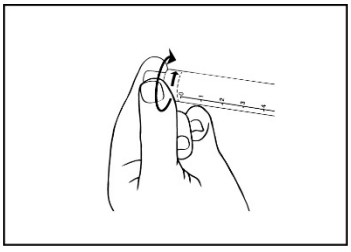
The product should not be used if the tamper evident seal on syringe (plastic cover to the end cap) is broken.

The external surface of syringe is sterile until blister is opened.

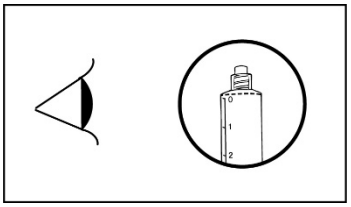
1) Withdraw the pre-filled syringe from the sterile blister.



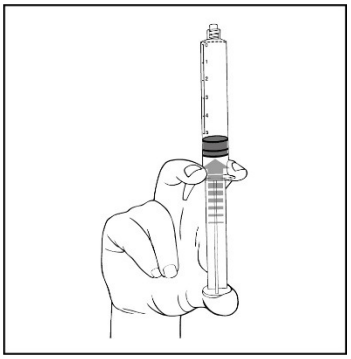
2) Push on the plunger to free the bung.



3) Twist off the end cap to break the seal.



4) Check the syringe seal (plastic cover to the end cap and seal under end cap) has been completely removed. If not, replace the cap and twist again.



5) Expel the air by gently pushing the plunger.

6) Connect syringe to vascular access device or to needle.
Push the plunger to inject the required volume.

The needle gauge appropriate for use with the syringe are 23 to 20 gauge for IV administration and 23 to 21 gauge for IM administration.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER
LABORATOIRE AGUETTANT 1, rue Alexander Fleming, 69007 Lyon, France

8. MARKETING AUTHORIZATION HOLDER
MBI Pharma, POB 5061, Kadima

9. MARKETING AUTHORIZATION NUMBER
175-53-36801-99

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