SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Atropine sulfate 0.5 mg/5 ml, solution for injection in pre-filled syringe

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 excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

Clear and colourless solution.

pH 3.2 – 4.0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Atropine sulfate 0.5 mg/5 ml, solution for injection in pre-filled syringe is indicated in adults and in paediatric population from birth, but with a body weight superior to 3 kg (see section 4.2).

- As a pre-anaesthetic medication to prevent vagal reactions associated with tracheal intubation and surgical manipulation,

- To limit the muscarinic effects of neostigmine, when given postsurgically to counteract non-depolarising muscle relaxants
- Treatment of hemodynamically compromising bradycardia and/ or atrioventricular block due to excessive vagal tone in emergency situation
- Cardiopulmonary resuscitation: to treat symptomatic bradycardia and AV block

As antidote following overdosage or poisoning with acetylcholinesterase-inhibitors e.g. anticholinesterases, organophosphorus, carbamates and muscarinic mushrooms

4.2 Posology and method of administration

Atropine sulfate 0.5 mg/5 ml, solution for injection in pre-filled syringe must be administered under medical supervision.

Posology:

Pre-anaesthetic medication

Intravenous administration immediately before surgery; if necessary an intramuscular administration 30-60 minutes before surgery is possible.

Adults:

0.3 – 0.6 mg IV (3 – 6 ml)

Paediatric population:

The usual dose in children is between 0.01-0.02 mg/kg body weight (maximum 0.6 mg per dose), dosage should be adjusted according to the patient's response and tolerance.

In combination with neostigmine to limit its muscarinic effects:

Adults:

0.6-1.2 mg IV (6 to 12 ml)

Paediatric population

0.02 mg/kg IV

Treatment of hemodynamically compromising bradycardia, atrioventricular block, cardiopulmonary resuscitation:

Adults:

- Sinus bradycardia: 0.5 mg IV (5ml), every 2-5 minutes until the desired heart rate is achieved.
- AV block: 0.5 mg IV (5ml), every 3-5 minutes (maximum 3 mg)

Paediatric population

0.02 mg/kg IV in a single dose (maximum dose 0.6 mg).

As an antidote to organophosphates (pesticides, nerve gases), to cholinesterase inhibitors and in muscarinic mushroom poisoning:

Intravenous use.

Adults:

0.5 - 2 mg atropine sulfate (5 - 20 ml), can be repeated after 5 minutes and subsequently every 10-15 minutes as required, until signs and symptoms disappear (this dose may be exceeded many times).

Paediatric population:

0.02 mg atropine sulfate/kg body weight possibly repeated several times until signs and symptoms disappear.

Dose adjustments

In general, dosage should be adjusted according to patient's response and tolerance.

Dosage to a total maximum dose of 3 mg in adults and 0.6 mg in children is usually increased until adverse effects become intolerable; then a slight reduction in dosage generally yields the maximum dosage tolerated by the patient.

Paediatric Population

This medicinal product is not appropriate to deliver a dose of less than 0.5 ml and should therefore not be used in neonates for which the body weight is inferior to 3 kg (see section 4.1).

The dosage ranges for the paediatric weight groups as stated below are values for guidance. The usual dose in children is between 0.01-0.02 mg/kg body weight (maximum 0.6 mg per dose), dosage should be adjusted according to the patient's response and tolerance.

Body weight (kg)	**Dose of 0.01 mg/kg body weight** Atropine sulfate 0.5 mg/5 ml Solution for Injection (ml)	**Dose of 0.02 mg/kg body weight** Atropine sulfate 0.5 mg/5 ml

		Solution for Injection (ml)
3 - 5	0.5 ml	0.5-1.0 ml
5-10	0.5-1.0 ml	1.0-2.0 ml
10 - 15	1.0-1.5 ml	2.0-3.0 ml
15 - 20	1.5-2.0 ml	3.0-4.0 ml
20 - 30	2.0-3.0 ml	4.0-6.0 ml
30 - 50	3.0-5.0 ml	6.0 ml

Special populations

Caution is advised for patients with renal or hepatic impairment and in elderly (see section 4.4).

Method of administration

Atropine 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 substance or to any of the excipients
- Closed-angle glaucoma
- Risk of urinary retention because of prostatic or urethral disease
- Achalasia of the esophagus, paralytic ileus, and toxic megacolon

All these contra-indications are however not relevant in life-threatening emergencies (such as bradyarrhythmia, poisoning).

4.4 Special warnings and precautions for use

Use with caution in case of:

- Prostatic enlargement
- Renal or hepatic insufficiency
- Cardiac insufficiency, arrhythmias, hyperthyroidism
- Chronic obstructive pulmonary disease, as a reduction in bronchial secretions may lead to the formation of bronchial plugs
- Intestinal atonia in elderly
- Pyloric stenosis
- Fever, or when ambient temperature is high

- In children and elderly, who may be more susceptible to its adverse effects
- In reflux oesophagitis, as atropine may delay gastric emptying, decrease gastric motility and relax oesophageal sphincter

Atropine should not be given to patients with myasthenia gravis unless given in conjunction with anticholinesterase.

Atropine administration should not delay implementation of external pacing for unstable patients, particularly those with high-degree (Mobitz type II second-degree or third-degree) block.

Antimuscarinics block vagal inhibition of the SA nodal pacemaker and should thus be used with caution in patients with tachyarrhythmias, congestive heart failure or coronary heart disease.

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

Combinations to be taken into account

Other drugs with anticholinergic activity, such as tricyclic antidepressants, some H1-antihistamines, antiparkinsonian drugs, disopyramide, mequitazine, phenothiazines, neuroleptic drugs, atropinic antispasmodics, clozapine and quinidine, because of the risk of potentialisation of atropinic adverse effects (urinary retention, constipation, dry mouth).

4.6 Fertility, pregnancy and lactation

Pregnancy

Data on a limited number of exposed pregnancies indicate no adverse effects of atropine on pregnancy or on the health of the fetus/new-born child.

Animal studies did not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Studies of the pharmacokinetics of atropine in mother and fetus in late pregnancy indicated that atropine rapidly crosses the placental barrier. Intravenous administration of atropine during pregnancy or at term may cause tachycardia in the fetus and the mother.

Atropine should not be used during pregnancy unless clearly necessary.

Breast-feeding

Small amounts of atropine may pass into human breast milk. Infants have an increased sensitivity to the anticholinergic effects of atropine. Atropine may inhibit the production of milk, particularly upon 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 it is decided during treatment to continue breastfeeding, the child should be monitored for anticholinergic effects.

Fertility

There are no data on effects of this atropine sulfate on fertility in humans. Atropine sulfate reduced fertility in male rats, presumably as a consequence of an inhibitory effect on the transport of sperm and semen during the process of emission.

4.7 Effects on ability to drive and use machines

Atropine may cause confusion or blurred vision and patients should be advised of it.

4.8 Undesirable effects

The pattern of adverse effects seen with atropine can mostly be related to their pharmacological actions at muscarinic and, at high doses, nicotinic receptors. Adverse effects are dose-related and usually reversible when therapy is discontinued. The most common effects occurring with relatively small doses are visual disturbances, reduced bronchial secretion, dry mouth, constipation, reflux, flushing, difficulty in micturition and dryness of the skin. Transient bradycardia may develop followed by tachycardia, with palpitations and arrhythmias.

The evaluation of adverse reactions is based on the following definition of frequency:

Very Common: ≥1/10;

Common: ≥1/100 to <1/10;

Uncommon: ≥1/1,000 to <1/100;

Rare: ≥1/10,000 to <1/1,000;

Very rare: <1/10,000;

Not known: cannot be estimated from the available data

Frequency / System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very Rare (<1/10,000)	Not known (cannot be estimated from the available data)
Immune system disorders				Allergic reactions	Anaphylaxis	
Nervous system disorders		Excitement, incoordination, mental confusion, and/or hallucinations (especially with higher dosages), hyperthermia	Psychotic reactions	Seizure, drowsiness		Headache, restlessness, ataxia, insomnia
Eye disorders	Visual disturbances (mydriasis, inhibition of accommodation, blurred vision, photophobia)					
Cardiac disorders		Tachycardia (arrhythmias, transient exacerbation of bradycardia)			Atrial arrhythmias, ventricular fibrillation, angina, hypertensive crisis	
Vascular disorders		Flushing				
Respiratory, thoracic and mediastinal disorders	Reduced bronchial secretion					

Frequency / System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very Rare (<1/10,000)	Not known (cannot be estimated from the available data)
Gastrointestinal disorders	Dryness of the mouth (difficulty in swallowing and talking, thirst), parasympathetic inhibition of gastrointestinal tract (constipation and reflux), inhibition of gastric secretion, loss of taste, nausea, vomiting, bloated feeling					
Skin and subcutaneous tissue disorders	Anhidrosis, urticaria, rash					
Renal and urinary disorders		Inhibition of the parasympathetic control of the urinary bladder, urinary retention				

Paediatric population

Infants, children and children with spastic paralysis or brain damage may be more susceptible to antimuscarinic effects.

Special populations

Atropine may cause excitement, incoordination, confusion and/or hallucinations especially in the elderly. An epidemiological study similarly reported lower cognitive performance in elderly patients receiving antimuscarinics.

Patients with Down syndrome may be more susceptible to antimuscarinic effects.

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. Healthcare professionals are asked to report any suspected adverse reactions via:

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms:

Flushing and dryness of the skin, dilated pupils with photophobia, dry mouth and tongue accompanied by a burning sensation, difficulty in swallowing, tachycardia, rapid respiration, hyperpyrexia, nausea, vomiting, hypertension, rash and excitement. Symptoms of CNS stimulation include restlessness, confusion, hallucinations, paranoid and psychotic reactions, incoordination, delirium and occasionally convulsions. In severe overdose, drowsiness, stupor and CNS depression may occur with coma, circulatory and respiratory failure and death.

Treatment:

Treatment should be supportive. An adequate airway should be maintained. Diazepam may be administered to control excitement and convulsions but the risk of CNS depression should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Belladonna alkaloids, tertiary amines.

ATC code: A03BA01.

Atropine is an antimuscarinic agent which competitively antagonises acetylcholine at postganglionic nerve endings, thus affecting receptors in the exocrine glands, smooth muscle, cardiac muscle and the central nervous system.

Peripheral effects include decreased production of saliva, sweat, nasal, lachrymal and gastric secretions, decreased intestinal motility and inhibition of micturition.

Atropine increases sinus rate and sinoatrial and AV conduction. Usually heart rate is increased, but there may be an initial bradycardia.

Atropine inhibits secretions throughout the respiratory tract and relaxes bronchial smooth muscle producing bronchodilation.

5.2 Pharmacokinetic properties

Absorption

Following intravenous administration, the peak increase in heart rate occurs within 2 to 4 minutes. Peak plasma concentrations of atropine after intramuscular administration are reached within 30 minutes, although peak effects on the heart, sweating and salivation may occur 1 hour after intramuscular administration.

Distribution

Plasma levels after intramuscular and intravenous injection are comparable at 1 hour. Atropine is distributed widely throughout the body and crosses the blood brain barrier and the placenta barrier.

Biotransformation

Atropine is incompletely metabolised in the liver and is excreted in the urine as unchanged drug and metabolites. About 50% of the dose is excreted within 4 hours and 90% in 24 hours.

Elimination

The elimination half-life is about 2 to 5 hours. Up to 50% of the dose is protein bound.

Paediatric Population

Children, particularly those younger than two years, may be more susceptible to the actions of atropine. The elimination half-life is more than doubled in children less than two years compared to adults.

Elderly

The elimination half-life of atropine is more than doubled in the elderly (>65 years old) compared to adults.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Atropine sulfate reduced fertility in male rats, presumably as a consequence of an inhibitory effect on the transport of sperm and semen during the process of emission.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Concentrated hydrochloric acid (for pH adjustment)

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened blister pack: 3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

5 ml solution in a pre-filled syringe (polypropylene) without needle, individually packaged in a transparent blister, available in box of 1, 5, 10, 12 or 20.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

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.

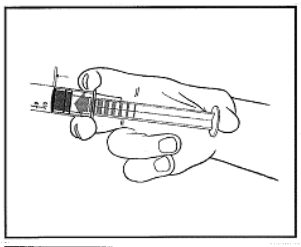
The content of un-opened and un-damaged blister is sterile, and must not be opened until used.

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.

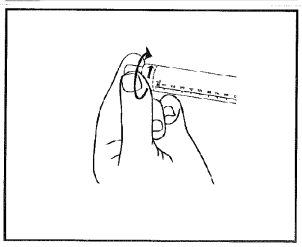
The product should not be used if the tamper evident seal on syringe (plastic cover to the end cap) is broken.

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

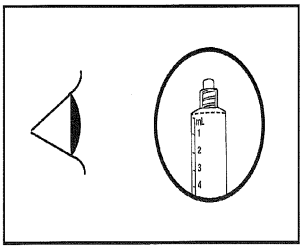
1) Withdraw the pre-filled syringe from the sterile blister.



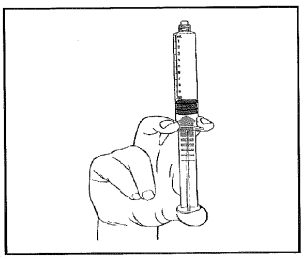
2) Push on the plunger to free the bung.



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 MARKETING AUTHORISATION HOLDER

LABORATOIRE AGUETTANT

1, rue Alexander Fleming

69007 Lyon

FRANCE

8 MARKETING AUTHORISATION NUMBER(S)

PL 14434/0034

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/01/2019

10 DATE OF REVISION OF THE TEXT

07/01/2019