# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Atropine Sulfate 600 micrograms/ml Solution for Injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains 600 micrograms of atropine sulfate.
For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection (Injection).
Clear, colourless, sterile, aqueous solution

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

In anaesthesia, as a parasympatholytic agent.

In the treatment of cholinergic crisis of myasthenia gravis.

In conjunction with neostigmine used to reverse the effects of non-depolarising muscle relaxants.

In the treatment of poisoning by certain cholinesterase inhibitors e.g. organo-phosphorous compounds.

During cardiopulmonary resuscitation to counteract excessive vagal tone on the heart.

### 4.2 Posology and method of administration

Posology

Use in anaesthesia
*Adults (including older people):*
The usual dose is 0.3 to 0.6mg intramuscularly or intravenously.

*Paediatric population:*
Premature infants: 65 micrograms
Full-term infants: 100 micrograms
6 - 12 months: 200 micrograms
Over one year: 10 - 20 micrograms/kg bodyweight

Treatment of cholinergic crisis of myasthenia gravis
*Adults:* The usual dose is 0.4 to 2.0 mg intravenously, which may be increased according to patient's response.

In conjunction with neostigmine used to reverse the effects of non-depolarising muscle relaxants
*Adults:* The usual dose is 0.6 to 1.2 mg given by slow intravenous injection. Atropine should be administered before neostigmine.

Treatment of poisoning by certain cholinesterase inhibitors
*Adults:* From 1.2 mg, increased according to patient's response.

Use during cardiopulmonary resuscitation
*Adults:* A dose of 0.2 to 0.5 mg may be given intravenously and repeated if necessary. Persistent bradycardia should be controlled by the insertion of a pacemaker as soon as possible.

Method of administration

Atropine Sulfate 600 micrograms/ml Solution for Injection may be administered by subcutaneous, intramuscular or intravenous injection.

**4.3 Contraindications**

Hypersensitivity to Atropine Sulfate or to any of the excipients listed in section 6.1.

Contra-indications are not applicable to the use of atropine in life-threatening emergencies (e.g. asystole).

Atropine is contraindicated in patients with obstruction of the bladder neck e.g. due to prostatic hypertrophy, reflux oesophagitis, closed angle glaucoma, myasthenia gravis (unless used to treat the adverse effects of an anticholinesterase agent), paralytic ileus, pyloric stenosis, severe ulcerative colitis and obstructive disease of the gastrointestinal tract.

**4.4 Special warnings and precautions for use**

Antimuscarinic agents should be used with caution in older people and children since these patients may be more susceptible to adverse effects. Atropine should also be used with caution in patients with hyperthyroidism, hepatic or renal disease or hypertension.

Use with caution in febrile patients or when ambient temperatures is high since antimuscarinics may cause an increase in temperature.

Great care is required when using atropine in the presence of acute myocardial ischaemia or infarction as these conditions may be worsened.

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.

Parenterally administered atropine should be used cautiously in patients with chronic pulmonary disease since a reduction in bronchial secretions may lead to formation of bronchial plugs. Antimuscarinics should be used with extreme caution in patients with autonomic neuropathy. Antimuscarinics decrease gastric motility, relax the lower oesophageal sphincter and may delay gastric emptying; they should therefore be used with caution in patients with gastric ulcer, oesophageal reflux or hiatus hernia associated with reflux oesophagitis, diarrhoea or GI infection.

**4.5 Interaction with other medicinal products and other forms of interactions**

The effect of the atropine may be enhanced by the concomitant administration of other drugs with anticholinergic activity e.g. tricyclic anti-depressants, antispasmodics, anti-parkinsonian drugs, amantadine, some anti-histamines, phenothiazines, disopyramide, quinidine, butyrophenones. By delaying gastric emptying, atropine may alter the absorption of other drugs.

During anaesthesia, the heart rate responsiveness to IV atropine could be decreased (and not effectively overcome by a large dose of atropine) when the subject is receiving concomitantly propofol; it could be due to propofol-induced suppression of the sympathetic nervous system.

An extreme caution should be observed when dobutamine-atropine stress echocardiography or the concomitant administration of a catecholamine with atropine has to be performed in patients who seem already extremely stressed or are in underlying hyperadrenergic state (risk of Tako-tsubo syndrome).

**4.6 Fertility, pregnancy and lactation**

Pregnancy

Atropine crosses the placenta. Studies in humans have not been done and only limited information is available from animal studies. Studies in animals have shown a teratogenic effect of atropine in one species with very high doses. Intravenous administration of atropine during pregnancy or at term may cause tachycardia in the foetus. Atropine should only be administered to pregnant women if the benefits outweigh the risks to the foetus.

Breast-feeding
Trace amounts of atropine appear in the breast milk and may cause antimuscarinic effects in the infant; lactation may be inhibited.

Fertility
Preclinical studies have shown atropine impaired fertility in male rats by inhibiting sperms and semen transportation from the vas deferens and seminal vesicle to the urethra during the process of emission. (see section 5.3)

**4.7 Effects on ability to drive and use machines**

Not applicable; this preparation is intended for use only in emergencies.

**4.8 Undesirable effects**

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: 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.

Adverse effects are dose-related and usually reversible when therapy is discontinued.

In relatively small doses, atropine reduces salivary, bronchial and sweat secretions; dry mouth and anhidrosis may develop, these effects being intensified as the dosage is increased.

Psychiatric disorders
Not known: hallucinations, mental confusionand/or excitement especially in the elderly.

Nervous system disorders
Not known: headache, nervousness, drowsiness, dizziness, insomnia.

Eye disorders
Not known: increased ocular tension, larger doses dilate the pupil and inhibit accommodation of the eye.

Cardiac disorders
Not known: larger doses block vagal impulses with consequent increase in heart rate with possible atrial arrhythmias, A-V dissociation and multiple ventricular ectopics ST elevation, acute myocardial infarction. There have been cases where severe bradycardia due to hyperkalaemia could not be resolved with atropine.

Vascular disorders
Not known: flushing.

Respiratory, thoracic and mediastinal disorders
Not known: reduced bronchial secretion may cause dehydration of residual secretion and consequent formation of thick bronchial plugs that are difficult to eject from the respiratory tract.

Gastrointestinal disorders
Not known: reduction of salivary secretions, parasympathetic inhibition of gastrointestinal tract, constipation, inhibition of gastric secretion, loss of taste, nausea, vomiting, bloated feeling, dysphagia, thirst.

Skin and subcutaneous tissue disorders
Not known: anaphylaxis, anhidrosis, urticaria and rashoccasionally progressing to exfoliation.

Musculoskeletal and connective tissue disorders
Not known: weakness.

Renal and urinary disorders
Not known: inhibition of the parasympathetic control of the urinary bladder, urinary retention.

**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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2. Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

**4.9 Overdose**

Symptoms:
Marked dryness of the mouth accompanied by a burning sensation, difficulty in swallowing, pronounced photophobia, flushing and dryness of the skin, raised body temperature, rash, nausea, vomiting, tachycardia and hypertension. Restlessness, tremor, confusion, excitement, hallucinations and delirium may result from CNS stimulation; this is followed by increasing drowsiness, stupor and general central depression terminating in death from circulatory and respiratory failure.

*Management*:
In severe cases, physostigmine, 1 to 4 mg, should be administered intravenously, intramuscularly or subcutaneously, the dose may be repeated if necessary since it is rapidly eliminated from the body. Diazepam may be administered for sedation of the delirious patient, but the risk of central depression occurring late in the course of atropine poisoning contraindicates large doses of sedative. An adequate airway should be maintained and respiratory failure may be treated with oxygen and carbon dioxide inhalation. Fever is reduced by the application of cold packs or sponging with tepid water. Adequate fluid intake is important. Urethral catheterization may be necessary. If photophobia is present or likely, the patient should be nursed in a darkened room.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Anticholinergic agents.

ATC code: A03BA01.

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

Pharmacodynamic effects
Peripheral effects include tachycardia, decreased production of saliva, sweat, bronchial, 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 bronchodilatation.

**5.2 Pharmacokinetic properties**

Absorption
Following intravenous administration, the peak increase in heart rate occurs within 2 to 4 minutes. Plasma levels after intramuscular and intravenous injection are comparable at one hour.

Distribution
Peak plasma concentrations of atropine after intramuscular administration are reached within 30 minutes, although peak effects on the heart, sweating and salivation may occur nearer one hour after intramuscular administration.

Atropine is distributed widely throughout the body and crosses the blood brain barrier.

Biotransformation
Atropine is metabolised in the liver by oxidation and conjugation to give inactive metabolites.

Elimination
The elimination half life is about 2 to 5 hours. Up to 50% of the dose is protein bound. It disappears rapidly from the circulation.

About 50% of the dose is excreted within 4 hours and 90% in 24 hours in the urine, about 30 to 50% as unchanged drug.

**5.3 Preclinical safety data**

Safety pharmacology & Repeat dose toxicity:
Large doses of atropine produced repeated daily inhibition of glandular secretions in puppies; a lethal cachexia was similar to that of fibrocystic disease of the pancreas. However, Pancreatic fibrosis and cyst formation were not produced.

Acute toxicity:
Acute toxicity of atropine induced two types of deaths in rabbits; convulsive deaths that were produced in young rabbits within half an hour of the intramuscular injection of a lethal dose of atropine sulfate ($LD_{50}$ ± S.E. 588 ± 85 mg. per kg., intramuscularly) and delayed deaths that occurred at a dose of 414 + 169 mg. per kg.

In young male albino rats intramuscular injection of lethal doses of atropine sulfate produced two types of death, an early hypothermic death ($LD_{50}$ ± SE of 1068 ± 77 mg/kg) and a delayed cachectic death (995 ± 61 mg/kg)In dogs, 1-3 mg of atropine produced mydriasis and bradycardia followed by transient increase in heart rate. Larger doses of 0.05 to 0.1 mg produced CNS depression, staggering gait, excitement, barking, tremor and convulsions particularly in hind legs, thirst and vomiting, depression, weakness and loss of appetite. Even larger doses paralyzed respiration and blocked spinal reflexes. Large repeat doses produced apathy, irritability, loss of appetite, vomiting and loss of weight.

Chronic toxicity:
Chronic toxicity of atropine was observed at a dose of 5 ± 3% of the $LD_{50}$ in a minimal number of young male rabbits after 100 days of daily intramuscular injection.

The clinical signs of toxicity included mydriasis, anorexia, impaired growth, oligodipsia, oliguria, fever, anemia, leucocytosis, hypocholesterolemia, and alkaluria.

The pathologic signs of toxicity included loss of weight and edema of most organs, hepatitis, pulmonary thrombosis, inhibition of spermatogenesis, thymic atrophy, and toxic changes in the gall bladder, spleen, and pancreas.

Sub-acute toxicity:
Subacute toxicity in a juvenile pygmy sperm whale (two doses of 0.01 mg/kg were given i.m., 12 hr apart, followed by three doses of 0.005 mg/kg i.m. s.i.d. over the next 3 days. Symptoms associated with atropine toxicity developed gradually and included hyper excitability, a generalized ascending paralysis of body musculature, shallow, rapid respiration, vomiting, aspiration of seawater, and pulmonary edema.

Carcinogenicity:
There are neither any reported results of tumor formation in male or female rats nor any literature available on studies conducted on either species of mice. There is therefore no data on TD50 values for Atropine; which is the daily dose rate in mg/kg body weight/day to induce tumors in half of the test animals that would have remained tumor free at zero dose.

Genotoxicity:
Atropine has been studied for its capacity to induce DNA damage and point mutations in bacteria and chromosomal aberrations in mammalian cells. With an exception of one study, the rest of these studies are deficient in the various aspects concerning development of relevant systems, dosage ranges, test methods and limited experience in the field of genetic toxicity. However, there has been one study which reported that atropine did not induce point mutations in Salmonella/microsome assay. This single negative result, however, cannot rule out the other genotoxic potential of atropine.

Reproduction:
Studies have shown atropine impaired fertility in male rats by inhibiting sperms and semen transportation from the vas deferens and seminal vesicle to the urethra during the process of emission.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Dilute Sulfuric Acid
Water for Injection

### 6.2 Incompatibilities

Atropine Sulfate is incompatible with alkalis.

### 6.3 Shelf life

Unopened: 4 years.
The product should be used immediately after opening.

### 6.4 Special precautions for storage

Do not store above 25°C. Keep ampoules in the outer carton in order to protect from light.

### 6.5 Nature and contents of container

1 ml, clear glass ampoules, glass Type I Ph. Eur.

Pack size: 10 x 1 ml ampoules.

### 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only.
Discard any unused content.

## 7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals (Ireland) Ltd
4045 Kingswood Road
Citywest Business Park
Co Dublin
Ireland

## 8 MARKETING AUTHORISATION NUMBER

PA0073/036/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1979

Date of last renewal: 01 April 2009

## 10 DATE OF REVISION OF THE TEXT

June 2020