AMINOPHYLLINE / DEMO INJECTION
250mg/10mL

COMPOSITION:
Each 10ml ampoule contains Aminophylline Hydrate 250mg. A clear, colorless to pale yellow solution.

ACTIONS & PHARMACOLOGY
Aminophylline , a complex of theophylline and ethylenediamine, has the action and uses of theophylline. It directly relaxes smooth muscles of the bronchial airways thus relieving bronchospasm, and has a stimulant effect on respiration.
Aminophylline relaxes the smooth muscles of blood vessels, decreases peripheral resistance and venous pressure, and causes diuresis. It also stimulates the myocardium and central nervous system. The exact mechanisms of these effects are unclear, and may be due to inhibition of phosphodiesterase resulting in increased intracellular cyclic AMP, adenosine receptor antagonism, prostaglandin antagonism, effects on intracellular calcium translocation or stimulation of endogenous catecholamines.
Aminophylline readily liberates theophylline in the body. Theophylline is metabolized in the liver, and the inactive metabolites are excreted mainly via the kidneys. In adults about 10% of the dose is excreted unchanged in the urine whereas in neonates about 50% is excreted unchanged. Hepatic metabolism is also affected by factors such as age, smoking, diseases, diet and drug interactions. The serum half-life of theophylline in otherwise healthy non-smoking adults is 7 to 9 hours, in children 3 to 5 hours, and in cigarette smokers 4 to 5 hours. The half-life may exceed 24 hours in premature infants, patients with chronic obstructive pulmonary disease, congestive heart failure or liver disease, and in older adults over 55 years of age.
Theophylline is approximately 60% bound to plasma proteins, but in neonates or adults with liver disease, plasma protein-binding is about 40%. The optimum therapeutic serum concentrations range from 10 to 20 µg per ml. Theophylline crosses the placenta and is distributed into breast milk.

INDICATIONS:
Bronchial asthma and chronic pneumonopathy obliterans (chronic obstructive diseases of the lungs), when bronchospasm is reversible

CONTRAINDICATIONS:
Contraindicated in patients with known hypersensitivity to aminophylline or its components (theophylline or ethylenediamine), or to xanthine derivatives.
Aminophylline is also contraindicated in patients with active peptic ulcer disease, hyperthyroidism, hypertension, cardiac arrhythymias, coronary artery disease, or other cardiovascular diseases, or uncontrolled seizure disorders, as these conditions may be exacerbated. It should not be given to patients with **congestive heart failure, impaired hepatic function, chronic alcoholism, acute febrile disease, severe hypoxia, cor pulmonale, bronchiolitis and chronic lung disease as theophylline clearance may be decreased in these conditions**.

PRECAUTIONS/WARNINGS:
Aminophylline should be given with caution to patients with history of peptic ulceration, hyperthyroidism, hypertension, cardiac arrhythymias, or other cardiovascular diseases, it should be used with caution in patients with impaired liver function, cardiac failure from any cause, chronic alcoholism, acute febrile illness, severe hypoxia, chronic lung disease, in neonates and in the elderly, as reduced theophylline clearance has been shown in these patients, resulting in increases in serum theophylline concentrations and serum half-life. Reduction of dosage and laboratory monitoring of serum theophylline concentrations may be appropriate under these circumstances.

Warnings
The likelihood of serious theophylline toxicity increases significantly when serum concentration exceeds 20 µg/ml. Serum levels above 20 µg/ml are rarely found after appropriate administration of the recommended doses. However, even conventional doses may result in excessive serum concentrations in patients with preexisting conditions that can cause reduced theophylline clearance (see: Precautions above).
Moreover, serious side-effects such as ventricular arrhythmias, convulsions or even death may appear as the first sign of toxicity without being preceded by milder side-effects. Thus, serum concentration monitoring is the only reliable method for predicting potentially life-threatening toxicity and should be carried out particularly in susceptible patient groups.
Use in pregnancy**:** It is not known whether aminophylline can cause fetal harm when administered to a pregnant woman. As such, it should be given to pregnant mothers only if clearly needed.
Use in lactation: Theophylline is distributed into breast milk and may cause irritability or other signs of toxicity in the nursing infant. As such, caution should be exercised when administering to nursing mothers, and the potential benefits versus potential risks to the nursing infant should be considered.
Use in elderly: Elderly patients may have reduced theophylline clearance and may require reduction in dosage or dosing frequency.
Use in children: Newborns, premature neonates and neonates have extremely slow clearance rates while older children have rapid clearance rates. As such, the dose of aminophylline should be adjusted

according to the age of the patient.

Drug interactions:

Aminophylline should not be administered concurrently with other xanthine derivatives or sympathomimetic agents, as the bronchodilator and toxic effects of these drugs are additive.

Theophylline clearance rate may be reduced by concomitant administration with other drugs including cimetidine, disulfiram, propranolol, macrolide antibiotics, quinolones, oral contraceptives and thiabendazole, thus requiring reduction in dose or dosing frequency. Decreased theophylline clearance may also be associated with influenza immunization or active influenza infection.

Phenytoin, phenobarbital and other anticonvulsants, rifampicin and cigarette smoking may increase theophylline clearance thereby necessitating increase in dose or dosing frequency.

Theophylline may increase the diuretic effects of thiazide diuretics and of furosemide.

Other drug interactions include the following:

Amiodarone, mexiletine : increase in serum theophylline levels, probably due to inhibition of its hepatic metabolism

Isoniazid : clearance and volume of distribution of theophylline were reduced and an increase in serum theophylline levels in healthy subjects after 14 days pretreatment with isoniazid

Allopurinol (high dose): increased serum theophylline levels

Ciprofloxacin : increased serum theophylline levels

Lithium carbonate: increased renal excretion of lithium

Drug-laboratory test interactions

The following drugs were found to interfere with the assay of theophylline by high-pressure liquid chromatography: acetazolamide, caffeine, some cephalosporins and penicillins, chloramphenicol, dimenhydrinate, paracetamol, procainamide, salicylates, some sulphonamides, theobromine, metronidazole. Drugs which interfere with spectrophotometric measurement of plasma-theophylline levels include: allopurinol, barbiturates, caffeine, carbamazepine, chiordiazepoxide, dicoumarol, frusemide, gentamicin, hydrochlorothiazide, hydroxyzine, morphine, phenytoin, probenecid, procainamide, salicylates, tetracycline, theobromine, thiopentone, warfarin. Enzyme immunoassay techniques are more specific and only caffeine and theobromine had been reported to interfere with substrate-labeled fluorescent immunoassays.

SIDE EFFECTS/ADVERSE REACTIONS:

The adverse effects of aminophylline include:

Gastrointestinal: nausea, vomiting, abdominal pain, diarrhea, gastrointestinal bleeding

Central Nervous System: insomnia, headache, irritability, anxiety, restlessness, dizziness, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions

Cardiovascular: tachycardia, palpitations, extrasystoles, flushing, hypotension, circulatory failure, ventricular arrhythmias.

Respiratory: tachypnea

Renal: potentiation of diuresis

Others: alopecia, hyperglycaemia, inappropriate ADH syndrome, rash

Plasma levels of theophylline above 20 µg/ml are associated with tremor, delirium, hyperthermia, tachycardia, tachypnoea, repeated vomiting with extreme thirst, diuresis, electrolyte disturbances, cardiac arrhythmias, convulsions and even death. Severe toxicity may not be preceded by milder symptoms. Too rapid intravenous injections may cause hypotension.

ROUTE OF ADMINISTRATION:

Aminophylline Injection should be administered intravenously.

DOSAGE:

Dosage should be adjusted according to individual response. To reduce the incidence of side-effects, the rate of intravenous aminophylline should not exceed 25 mg per minute. In patients who have not been receiving aminophylline or theophylline previously, a loading dose of 6 mg/kg bodyweight, diluted in isotonic sodium chloride or dextrose, should be given by slow intravenous injection over 20 to 30 minutes. In patients who have been receiving aminophylline or theophylline, the loading dose should be reduced to 3 mg/kg bodyweight. Alternatively, the serum theophylline concentration may be measured and the loading dose adjusted on the basis that aminophylline 6 mg/kg lean bodyweight can increase serum theophylline concentration by 1 µg/ml.

If necessary, a maintenance dose may be given by slow intravenous infusion after the loading dose. Suggested aminophylline intravenous maintenance dose are as follows, the dose being reduced after 12 hours:

Children 6 months to 9 years: Children 8 to 16 years and adult smokers:	1.2mg/kg bodyweight per hour, reduced to 1.0 mg/kg bodyweight per hour 1.0mg/kg bodyweight per hour, reduced to 800 µg/kg bodyweight per hour
Nonsmoking adults:	700 µg/kg bodyweight per hour, reduced to 500 µg/kg bodyweight per hour
Older patients or patients with lung disease:	600 µg/kg per hour, reduced to 300 µg/kg per hour
Patients with cardiac failure or liver disease:	500 µg/kg per hour, reduced to 100-200 µg/kg per hour.

Serum theophylline concentration monitoring is recommended and the maintenance dose reduced if serum concentrations exceed 20 µg/ml or if the patient experiences signs of toxicity.

Incompatibilities

Solutions of aminophylline is alkaline and when pH falls below 8, crystals of theophylline will deposit. Drugs which are known to be unstable in alkaline medium and those that will decrease pH to below the critical value should not be mixed with aminophylline injections. The addition of aminophylline to glucose injection has been reported to raise pH from 7.7 to 10.45, at which pH insulin and erythromycin gluceptate are incompatible. Other drugs which are incompatible with aminophylline include amiodarone, dobutamine, tetracycline hydrochloride, benzylpenicillin potassium.

OVERDOSAGE AND TREATMENT:

Symptoms of overdosage are usually associated with plasma theophylline levels in excess of 20pg/ml and include: tremor, delirium, hyperthermia, tachycardia, tachypnoea, repeated vomiting with extreme thirst, diuresis, electrolyte disturbances, cardiac arrhythmias, convulsions and even death.

Administration of oral activated charcoal (eg 0.5mg/kg up to 20g, every 2 hours), helps to increase the clearance of theophylline by absorption of theophylline secreted into the gastrointestinal fluids. Charcoal must be retained in, and pass through the gastrointestinal tract in order to be effective, hence it is recommended that emesis be controlled by administration of anti-emetics, where appropriate.

Symptomatic treatment should be instituted. Measures should be taken to monitor vital signs, maintain blood pressure and provide adequate hydration. Serum theophylline concentrations should be monitored. Charcoal haemoperfusion and haemodialysis may be required.

STORAGE:

Store below 30 °C. Protect from light.

Keep out of reach of children

Shelf-life: 3 years

PRESENTATION

10ml per plastic ampoule, 10 ampoules per carton box

MADE IN GREECE BY:

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