Aminophyllin IV Fresenius 250mg/10ml
Aminophylline 250mg in 10ml

Description
A clear, colourless to faintly yellow sterile solution, odourless or faintly ammoniacal in amber glass ampoules.

Composition
Each amber ampoule contains 250mg of Aminophylline.

Mode of Action
Aminopylline is a complex of Theophylline with ethylenediamine. It releases free Theophylline at physiological pH. Aminophylline anhydrous contains about 86% of anhydrous Theophylline (Aminophylline dehydrate contains about 79% of anhydrous Theophylline).

Theophylline has two distinct actions in the airways of patients with; smooth muscle relaxion resulting in bronchodilation, and suppression of the response of the airways to stimuli (ie non-bronchodilator prophylactic effects). Theophyllines also increase the force of contraction of diaphragmatic muscles. The exact mechanisms of action of Theophyllines are not known.

Summary of Pharmacodynamics and Pharmacokinetics
Theophylline distributes freely into fat-free tissues and is extensively metabolized in the liver.
The half-life of Theophylline varies consistently between individuals and with age. In neonates and infants up to 6 months of age the half-life exceeds 24 hours. In children (more than 6 months) Theophylline has a mean half-life of 3.7 hours. In adults the mean half-life is 8.7 hours. In cigarette smokers (20-40 cigarettes/day) the mean half-life is 4-5 hours.

In neonates approximately 50% of the Theophylline dose is excreted unchanged in the urine, but beyond three month old, only 10% is excreted in urine and active metabolites do not accumulate to clinically significant levels.

Indications
Aminophylline is used for the treatment of reversible bronchospasm associated with chronic bronchitis, emphysema, bronchial asthma and chronic obstructive pulmonary disease.

Side Effects/ Adverse reaction
The side-effects frequently encountered with Theophylline and its derivatives are gastro-intestinal irritation and stimulation of the central nervous system.

Theophyllines are irritating to the gastrointestinal tract: nausea, vomiting, heartburn, epigastric pain and intestinal bleeding.(less frequently-diarrhoea)

Central nervous system effects (more common in children): headache, irritability, restlessness, nervousness, tremor, insomnia, dizziness, seizures.

Less frequently:
Tachycardia, flushing, palpitations, hypotension, ventricular arrhythmias, tachypnoea.

Urinary frequency, dehydration, hyperglycaemia and mental depression. Elevated serum AST levels. Hypersensitivity reactions have occurred.

Ethylenediamine in aminophylline may cause hypersensitivity reactions including erythematous rash, pruritis, erythroderma and exfoliative dermatitis, hives, or sloughing of skin. Aminophylline can produce both immediate and delayed hypersensitivity reactions.

Warning/Precautions
Aminophylline should not be administered concurrently with ephedrine. Aminophylline should not be administered concurrently with other xanthine medications.

Paediatrics: use with extreme caution in neonates and young children as reduced clearance, resulting in increases in the serum Theophylline concentration and serum half life, increases the potential for toxicity. Hyperglycaemia has been reported in preterm infants. Do not administer repeated doses if the heart rate exceeds 180beats/min.

Elderly patients: use with caution at reduced dosages (by approximately 30%) in adults over 60 years, as reduced clearance increases the potential for toxicity.

Smokers: tobacco and dagga (marijuana) smoking increases Theophylline clearance by induction of metabolic pathways. Careful monitoring of serum Theophylline concentration should be undertaken in people who stop smoking.

Use with caution in patients undergoing influenza immunization or with acute viral infection such as influenza or those with sustained high fever as plasma Theophylline levels may be elevated as a result of reduced Theophylline clearance.

In individuals in whom Theophylline plasma clearance is reduced for any reason, even conventional doses may result in increased serum levels and potential toxicity. Those at risk due to reduced hepatic clearance include patients with:

- impairment liver function
- congestive cardiac failure
- chronic obstructive pulmonary disease or pneumonia
- chronic alcoholism
- patients more than 55 years of age
- particularly males and those with chronic lung disease
- sepsis with multiple organ failure
- shock.

Caution should be used in patients with the following conditions, as these conditions may be exacerbated:

- ischaemic heart disease
- hypertension
- hyperthyroidism
- epilepsy-unless controlled on anticonvulsants
- history of peptic ulcer disease
- glaucoma
- diabetes mellitus
- severe hypoxemia.

Caution should be used in angina pectoris, acute myocardial injury or pre-existing arrhythmias.

Plasma concentrations of theopylline greater than 20 mcg per ml are considered to be toxic.

Effect on the route of administration:
Rapid intravenous injection has produced dizziness, faintness, palpitations, syncope, precordial pain, flushing, profound bradycardia, extrasystoles, severe hypotension and cardiac arrest. Sudden deaths have been reported.

Intramuscular injection has produced intense local pain sloughing of tissue.
Do not use the solution if crystallization has occurred.

Special precaution
Careful consideration of the factors that alter Theophylline clearance should occur prior to initiation of the Theophylline therapy, prior to increases in Theophylline dose and during follow-up. Serum Theophylline measurements are advisable to determine whether the dose is appropriate, particularly

- When initiating therapy and to guide final dosage adjustments after titration.
- Before making a dose increase to determine whether the serum concentration is subtherapeutic in a patient who continues to be symptomatic.
- Whenever symptoms of Theophylline toxicity are present.
- Whenever there is a new illness, worsening of a chronic condition or a change in the patient's treatment that may alter Theophylline clearance.

To guide a dose increase, the blood sample should be taken at peak serum theophyline concentration; 1-2 hours after a dose at steady-state, and 4-6 hours after a delayed-release preparation. For most patients, steady-state will be reached after three days of dosing when no doses have been missed and no extra doses have been added. A trough concentration provides no useful information and may be misleading.

The patient should be instructed to seek medical advice whenever nausea, vomiting, persistent headache or rapid heartbeat occurs during treatment with Theophylline even if another cause is suspected. The patient should contact the doctor if they develop a new illness, experience worsening of a chronic illness, if they start or stop smoking cigarettes or dagga (marijuana), or if another doctor adds to, or discontinues previously prescribed medication. Patients must inform clinicians that they are taking Theophylline and not to alter the dose, the timing of the dose or the frequency of administration without first consulting their doctor.

Contraindication
Aminophylline is contraindicated in patients with hypersensitivity to Aminophylline. Hypersensitivity to any xanthines, such as Theophyllines, caffeine or theobromine. Porphyria. Active gastritis or active peptic ulcer disease.

Recommended Dose and Direction for Use.
Recommended doses are given as a guide only. Dosage must be individualised based on patient characteristics, clinical response, and steady state theophylline concentration. Doses should be calculated on lean (ideal) body weight. Oral theophylline therapy should be substituted for intravenous therapy as soon as adequate improvement has been made. For intravenous use only.

A loading dose is generally administered over 20-30 minutes, followed by a maintenance dose.

Adults and children 6 months and over:
For patients not currently undergoing aminophylline or theophylline therapy, a dose of 6 mg aminophylline/kg lean body weight should be infused over 20-30 minutes, to provide a peak serum theophylline concentration of approximately 10 microgram/mL (55 micromole/L).

For patients currently undergoing aminophylline or theophylline therapy, a serum theophylline concentration should be obtained. The dose of aminophylline may be administered on the principle that 0.6 mg aminophylline/kg lean body weight will increase the serum theophylline concentration by 1 microgram/mL. If it is not possible to obtain serum theophylline concentration, a dose of 3 mg aminophylline/kg lean body weight may be administered.

Patients	Loading dose mg aminophylline/kg	Maintenance dose mg aminophylline/kg	
		For next 12h	Beyond 12 h
Children 6 months to 9 years	6 (4.74)*	1.2 (0.95)*	1.0 (0.79)*
Children 9 to 16 years	6 (4.74)*	1.0 (0.79)*	0.8 (0.63)*
Young adult smokers	6 (4.74)*	1.0 (0.79)*	0.8 (0.63)*
Non-smoking adults	6 (4.74)*	0.7 (0.55)*	0.5 (0.4)*
Older patients or those with cor pulmonae	6 (4.74)*	0.6 (0.47)*	0.3 (0.24)*
Patients with congestive heart failure or hepatic failure	6 (4.74)*	0.5 (0.4)*	0.1-0.2 (0.08-0.16)*

* Figures in brackets are the equivalent doses of anhydrous theophylline

Incompatibility
Aminophylline should be dilute in sodium chloride 0.9% infusion only.

Use in Pregnancy and Lactation
Pregnancy category Aminophylline are no evidence that it is unsafe but the pharmacokinetics may be altered, so close therapeutic drug monitoring is recommended. Neonates of mothers on Theophylline should be monitored as they may show apnoea, tachycardia, irritability and vomiting.
Theophylline is excreted in breast milk and is present at concentrations equivalent to that in maternal serum. Irritability and insomnia in the infant have been reported.

Interaction with Other Medicaments/Drug Interactions
Agents which increase the Theophylline clearance, resulting in a lower plasma Theophylline concentration, may require an increased dose of Theophylline.

Smokers may require larger doses as Theophylline clearance is increased. Hepatic enzyme-including agents may increase the dose needed to produce therapeutic effect: alcohol, aminoglutethimide, barbiturates, rifampicin, phenytoin, carbamazepine, sulphinpyrazone, lithium, meprobamate, moricizine, intravenouse isoproterenol, propranolol, tacrine.

Agents which decrease the Theophylline clearance resulting in a higher Theophylline plasma concentration, increase the potential for side effects.

Agents that diminish hepatic biotransformasion and result in raised Theophylline levels: Cimetidine, fluvoxamine, ranitidine, macrolide antibiotics (erythromycin, lincomycin, clarithromycin, troleandomycin), fluoroquinolone antibiotics (ciprofloxacin, ofloxacin, norfloxacin, enoxacin, penfloxacin), fluconazole, thiabendazole, allapurinol, interferon, isoniazid, disulfuram, viloxazine, beta-blockers, calcium channel blockers, mexiletina, tacrine, oral contraceptives, pentoxiphylline, ticlopidine, verapamil, methotrexate, oestrogen-containing contraceptives.

Concomitant use with sympathomimetic agents may increase the potential for cardiotoxicity particularly in cases of severe asthma with marked hypoxia.

Hypokalaemia associated with the administration of beta2-adrenergic stimulants and diuretics may be potentiated by xanthine derivatives.

The toxic potential of cardiac glycosides and reserpine may be increased.

Ventricular arrythmias have been reported when halothane is used concurrently with Theophylline.

Ketamine - concurrent use may lower the seizure threshold.

Xanthine derivatives may antagonize the neuromuscular blocking activity of Pancuronium.

Sucralfate may adsorb Theophylline derivatives if medications are administered less than two hours apart.

Benzodiazepines – large doses may be needed to produce the desired level of sedation.

Chlordiazepoxide – induced fatty acid mobilization may be aggravated.

Furosemide – induced diuresis may be increased.

Lithium excretion by the kidneys is increased and higher doses may be required if given Theophylline.

Symptoms and Treatment of Overdose
Theophylline has a low therapeutic index. Serious side effects such as ventricular arrhythmias or convulsions may appear as the first sign of toxicity without any previous warning. All patients suspected of overdosage should be hospitalized.

Sign and symptoms of overdosage are related primarily to the cardiovascular, gastrointestinal and central nervous systems.

Serum levels of >165 micromoles/L (30 micrograms/ml) are associated with clinical intoxication. Patients who experience acute overdosage are less likely to develop seizures than those with a chronic overdose unless the serum Theophylline levels is >550 micromoles/L (100 microgram/ml). after chronic overdosage, generalized seizures, life threatening arrhythmias and death may occur at serum levels of > 165 micromoles/L (30 microgram/ml).

Tachycardia is an early sign of toxicity. Anorexia, nausea, vomiting, abdominal pain, diarrhea, insomnia, irritability, restlessness, and headache commonly occur. Other early signs include confusion, agitated or manical behaviour, extreme thirst, fever, tinnitus, palpitations and arrhythmias. Hypotension and metabolic disturbances such as hyperglycaemia, hypokalaemia, hypophosphataemia, hypercalcaemia and acidosis or chemical alkalosis occur. May progress to delirium, muscle twitching, profuse sweating, severe dehydration and hyperthermia. Significant morbidity is due to the development of arrythmias or convulsions.

Treatment of overdosage:
Emptying of the stomach is generally not necessary if the patient has vomited. Emesis using ipecac syrup should generally be avoided in the management of the Theophylline overdosage. If there has been no vomiting and seizures have not occurred, the stomach should be emptied by lavage. If seizures have occurred, the airway should be protected during lavage with a cuffed endotracheal tube. Lavage should be followed by administration of activated charcoal and a cathartic (particularly if an extended-release preparation has been taken). Repeated doses of activated charcoal increase clearance and should be given until toxicity resolves. The progress of toxicity should be monitored by repeated Theophylline serum concentration measurement. Monitoring of the ECG, electrolytes and blood sugar is important.

Seizures associated with Theophylline toxicity are often resistant to anticonvulsant therapy and may result in irreversible brain injury if not rapidly controlled. Death is most commonly secondary to cardiorespiratory arrest and/or hypoxic encephalopathy following prolonged generalized seizures or intractable cardiac arrhythmias causing haemodynamic compromise. The need for anticonvulsant therapy in patients at risk of developing seizures should be anticipated. Treatment of seizures should be rapid and aggressive. Seizures should be controlled with diazepam.

In heart failure or liver disease, refer to a specialist. Haemodialysis or charcoal haemoperfusion may be necessary.

Presentation
The injection is available in 10ml amber ampoule.Ten ampoules are packed into one outer carton.

Storage Condition
Protect from light and store below 30°Celsius. Keep out of reach of children.

Shelf Life
The injections can be used within 48 months from the date of manufacture if kept as recommended.

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