AMINO-100 TABLETS
(Vardhman Exports),

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AMINO-100mg TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Aminophylline BP 100 mg

Excipients with known effects:

Each tablet contains 50 mg of Dibasic calcium phosphate, 4 mg of Magnesium Stearate.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

White, circular, flat, uncoated tablet embossed 'AMINO' on one side and breakline on other side of each tablet.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Amino-100 tablets are indicated for use in adults and children aged above 6 years.

For the treatment and prophylaxis of bronchospasm associated with asthma, chronic obstructive pulmonary disease and chronic bronchitis. Also indicated in adults for the treatment of left ventricular and congestive cardiac failure.

Aminophylline should not be used as the first drug of choice in the treatment of asthma in children.

4.2 Posology and method of administration

Posology

Adults and the elderly:

The usual maintenance dose is one Amino-100 mg tablet twice daily. This may be titrated to higher dosage as required.

Paediatric population aged above 6 years:

The usual paediatric maintenance dose is 10 mg/kg twice daily.

Some children with chronic asthma require and tolerate much higher doses (11-18 mg/kg twice daily).

Clearance is increased in children compared to values observed in adult subjects. The rapid clearance observed in children decreases towards adult values in late teens. Therefore lower dosages may be required for adolescents.

Aminophylline distributes poorly into body fat, therefore, mg/kg doses should be calculated on the basis of lean (ideal) body weight.

Plasma aminophylline concentrations should ideally be maintained between 5 and 12 mcg/mL. A plasma level of 5 mcg/mL probably represents the lower level of clinical effectiveness. Significant adverse reactions are usually seen at plasma aminophylline levels greater than 20 mcg/mL. Monitoring of plasma aminophylline concentrations may be required when: higher doses are prescribed; patients have co-morbidities resulting in impaired clearance; when aminophylline is co-administered with medication that reduces aminophylline clearance.

Method of administration

Oral

The tablets should be swallowed and not chewed.

4.3 Contraindications

Hypersensitivity to xanthines, ethylene diamine or any of the excipients listed in section 6.1.

Concomitant use with ephedrine in children less than 6 years of age (or less than 22 kg)

Porphyria.

Aminophylline is contraindicated in children under 6 months of age.

4.4 Special warnings and precautions for use

The patient's response to therapy should be carefully monitored – worsening of asthma symptoms requires medical attention.

Due to potential decreased clearance, dose reduction and monitoring of serum aminophylline concentrations may be required in elderly patients and patients with:

• cardiac disease

• hepatic disease

• exacerbations of lung disease

• hypothyroidism (and when starting acute treatment)

• fever

• viral infections

Due to potential increased clearance, dose increase and monitoring of serum aminophylline concentrations may be required in patients with hyperthyroidism (and when starting acute hyperthyroidism treatment) and cystic fibrosis.

Aminophylline may:

• act as a gastrointestinal tract irritant and increase gastric secretion, therefore caution should be exercised in patients with peptic ulcers.

• exacerbate cardiac arrhythmias and therefore caution should be exercised in patients with cardiac disorders

• exacerbate frequency and duration of seizures and therefore caution should be exercised in patients with history of seizures and alternative treatment considered.

Caution should be exercised in elderly males with pre-existing partial urinary tract obstruction, such as prostatic enlargement, due to risk of urinary retention.

Particular care is advised in patients suffering from severe asthma who require acute aminophylline administration. It is recommended that serum aminophylline concentrations are monitored in such situations.

Caution should also be used in patients with, severe hypertension or chronic alcoholism.

4.5 Interaction with other medicinal products and other forms of interaction

The following increase clearance of aminophylline and it may therefore be necessary to increase dosage to ensure a therapeutic effect: aminoglutethimide, carbamazepine, isoprenaline, phenytoin, rifampicin, sulphinpyrazone, barbiturates, ritonavir and hypericum perforatum (St. John's Wort).

Smoking and alcohol consumption can also increase clearance of aminophylline.

The following reduce clearance of aminophylline and a reduced dosage may therefore be necessary to avoid side-effects: aciclovir, allopurinol, carbimazole, cimetidine, clarithromycin, diltiazem, disulfiram, erythromycin, fluconazole, interferon, isoniazid, methotrexate, mexiletine, nizatidine, pentoxifylline, propafenone, propranolol, thiabendazole, verapamil and oral contraceptives.

Aminophylline has been shown to interact with some quinolone antibiotics including ciprofloxacin and enoxacin, which may result in elevated plasma aminophylline levels.

The concomitant use of aminophylline and fluvoxamine should usually be avoided. Where this is not possible, patients should have their aminophylline dose reduced and plasma aminophylline should be monitored closely.

Factors such as viral infections, liver disease and heart failure also reduce aminophylline clearance. There are conflicting reports concerning the potentiation of aminophylline by influenza vaccine and physicians should be aware that interaction may occur resulting in increased serum aminophylline levels. A reduction of dosage may be necessary in elderly patients. Thyroid disease or associated treatment may alter aminophylline plasma levels.

Concurrent administration of aminophylline may:

• inhibit the effect of adenosine receptor agonists (adenosine, regadenoson, dipyridamol) and may reduce their toxicity when used for cardiac perfusion scanning;

• oppose the sedatory effect of benzodiazepines;

• result in the occurrence of arrhythmias with halothane;

• result in thrombocytopenia with lomustine;

• increase urinary lithium clearance.

Therefore these drugs should be used with caution.

Care should be taken in its concomitant use with β-adrenergic agonists, glucagon and other xanthine drugs, as these will potentiate the effects of aminophylline. The incidence of toxic effects may be enhanced by the concomitant use of ephedrine.

Hypokalaemia resulting from β2 agonist therapy, steroids, diuretics and hypoxia may be potentiated by xanthines. Particular care is advised in patients suffering from severe asthma who require hospitalisation. It is recommended that serum potassium concentrations are monitored in such situations.

4.6. Fertility, Pregnancy and lactation

Pregnancy

There are no adequate data from well controlled studies from the use of aminophylline in pregnant women. Aminophylline has been reported to give rise to teratogenic effects in mice, rats and rabbits (see section 5.3). The potential risk for humans is unknown.

Aminophylline should not be administered during pregnancy unless clearly necessary.

Breast-feeding

Aminophylline is secreted in breast milk, and may be associated with irritability in the infant, therefore it should only be given to breast feeding women when the anticipated benefits outweigh the risk to the child.

4.7 Effects on ability to drive and use machines

Amino-100mg tablets have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The following adverse drug reactions have been reported in the post-marketing setting for aminophylline. Frequencies of "not known" have been assigned as accurate frequencies cannot be estimated from the available clinical trial data.

System Organ Class	**Frequency not known (cannot be estimated from the available data)**
Immune system disorders	Anaphylactic reaction
	Anaphylactoid reaction
	Hypersensitivity
Metabolism and nutrition disorders	Hyperuricaemia
Psychiatric disorders	Agitation
	Anxiety
	Insomnia
	Sleep disorder
Nervous system disorders	Convulsions
	Dizziness
	Headache
	Tremor
Cardiac disorders	Atrial tachycardia
	Palpitations
	Sinus tachycardia
Gastrointestinal disorders	Abdominal pain
	Diarrhoea
	Gastric irritation
	Gastro-oesophageal reflux
	Nausea
	Vomiting
Skin and subcutaneous tissue disorders	Pruritus
	Rash
Renal and urinary disorders	Diuresis
	Urinary retention*

* Please refer to section 4.4 as aminophylline may induce urinary retention in elderly males with pre-existing partial urinary tract obstruction.

Reporting of 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.

4.9 Overdose

Aminophylline has a low therapeutic index. Aminophylline toxicity is most likely to occur when serum concentrations exceed 20 micrograms/ml and becomes progressively more severe at higher serum concentrations.

Over 3 g could be serious in an adult (40 mg/kg in a child). The fatal dose may be as little as 4.5 g in an adult (60 mg/kg in a child), but is generally higher.

Symptoms

Warning: Serious features may develop as long as 12 hours after overdosage with prolonged release formulations.

Alimentary symptoms: Nausea, vomiting (which is often severe), epigastric pain and haematemesis. Consider pancreatitis if abdominal pain persists.

Neurological symptoms: Restlessness, hypertonia, exaggerated limb reflexes, convulsions, seizures. Coma may develop in very severe cases.

Cardiovascular symptoms: Hypotension. Sinus tachycardia is common. Ectopic beats and supraventricular and ventricular tachycardia may follow.

Metabolic symptoms: Hypokalaemia due to shift of potassium from plasma into cells is common, can develop rapidly and may be severe. Hyperglycaemia, hypomagnesaemia and metabolic acidosis may also occur. Rhabdomyolysis may also occur.

Management

Activated charcoal or gastric lavage should be considered if a significant overdose has been ingested within 1-2 hours. Repeated doses of activated charcoal given by mouth can enhance Aminophylline elimination. Measure the plasma potassium concentration urgently, repeat frequently and correct hypokalaemia. BEWARE! If large amounts of potassium have been given, serious hyperkalaemia may develop during recovery. If plasma potassium is low, then the plasma magnesium concentration should be measured as soon as possible.

In the treatment of ventricular arrhythmias, proconvulsant antiarrhythmic agents such as lignocaine (lidocaine) should be avoided because of the risk of causing or exacerbating seizures.

Measure the plasma Aminophylline concentration regularly when severe poisoning is suspected, until concentrations are falling. Vomiting should be treated with an antiemetic such as metoclopramide or ondansetron.

Tachycardia with an adequate cardiac output is best left untreated. Beta-blockers may be given in extreme cases but not if the patient is asthmatic. Control isolated convulsions with intravenous diazepam. Exclude hypokalaemia as a cause.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airways diseases, xanthines.

ATC code: R03DA05

Aminophylline is a bronchodilator. In addition it affects the function of a number of cells involved in the inflammatory processes associated with asthma and chronic obstructive airways disease. Of most importance may be enhanced suppressor, T-lymphocyte activity and reduction of eosinophil and neutrophil function. These actions may contribute to an anti-inflammatory prophylactic activity in asthma and chronic obstructive airways disease.

Aminophylline stimulates the myocardium and produces a diminution of venous pressure in congestive heart failure leading to marked increase in cardiac output.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of Amino-100 tablets, the delivery of Aminophylline is controlled and at steady state, peak concentrations are typically seen after approximately 5 hours.

An effective plasma concentration is considered to be 5-12 micrograms/ml, although plasma concentrations up to 20 micrograms/ml may be necessary to achieve efficacy in some cases. Do not exceed 20 micrograms/ml.

Distribution and Protein Binding

Aminophylline is distributed through all body compartments; approximately 60% is bound to plasma proteins.

Biotransformation

Aminophylline is metabolised in the liver to 1, 3 dimethyluric acid, 1 methyluric acid and 3–methylxanthine.

Elimination

Aminophylline and its metabolites are excreted mainly in the urine. Approximately 10% is excreted unchanged.

Factors affecting clearance

The predominant factors which alter Aminophylline clearance are: age, body weight, diet, smoking habits, other drugs and cardiorespiratory or hepatic disease. Clearance is increased in children compared to values observed in adult subjects. Clearance decreases towards adult values in late teens.

5.3 Preclinical safety data

Genotoxicity and Carcinogenicity

In vitro and *in vivo* assays, have shown both positive and negative genotoxic results for Aminophylline. However, oral Aminophylline administered daily to rats and mice for 2 years did not show carcinogenicity. Therefore, it is unlikely that Aminophylline poses a carcinogenic risk in man.

Reproductive and Developmental Toxicity

Aminophylline has been shown to have effects upon the male reproductive system in rodents, but at doses considered in excess of the maximum human dose indicating little relevance to clinical use.

Several embryofetal development studies in rats, mice and rabbits have demonstrated developmental effects independent from maternal toxicity at high doses of Aminophylline. Therefore Aminophylline should be considered to have the potential for developmental toxicity in man.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch,
Dibasic calcium phosphate,
Methyl Paraben,
Propyl Paraben,
Colloidal silicon Dioxide,
Purified Talc,
Sodium Starch Glycollate,
Magnesium Stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a cool place and protect from light. Keep all medicines out of reach of children.

6.5 Nature and contents of container

1000 tablets sealed in a black colour PP bag and packed in 400ml Amber colour bottle with 2 silica and one literature sealed with golden plastic cap.

6.6 Special precautions for disposal and other handling

No special requirements.

7. APPLICANT/MANUFACTURER

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