

ANGEL BIOGENICS PVT. LTD.

DOSSIER FOR RWANDA

AMINOPHYLLINE TABLETS BP 100 MG

1.4 Product Information

1.4.1 Prescribing information (Summary of Product Characteristics)

Enclosed below;

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SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

AMINOPHYLLINE TABLETS BP 100 MG

2. Qualitative and quantitative composition

Each film coated tablet contains:

Aminophylline BP

Eq. to Anhydrous Aminophylline...100 mg

Excipients....Q.S

Colour: Red oxide of Iron

3. Pharmaceutical form

Tablets

4. Clinical particulars

4.1 Therapeutic indications

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

Dosing is based on patient's ideal body weight. In adults a loading dose of 5.7 mg/kg administered intravenously over 30 minutes followed by a continuous maintenance infusion of 0.5 mg/kg/hr for non-smokers 60 years or younger and 0.38 mg/kg/hour for those 60 years and older.

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Method of administration

Oral

The tablets should be swallowed and not chewed.

Missed dose

If a patient forgets to take a dose but remembers within 4 hours of the time the dose was due to be taken, the tablets can be taken straight away. The next dose should be taken at the normal time. Beyond 4 hours, the prescriber may need to consider alternative treatment until the dose is due.

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.

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- 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, sulphapyrazone, 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.

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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 β_2 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.

Aminophylline may decrease steady state phenytoin levels.

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

Tablets have no or negligible influence on the ability to drive and use machines.

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4.8 Undesirable effects

If you experience any of the following serious side effects, stop taking aminophylline and seek emergency medical attention:

An allergic reaction (difficulty breathing; closing of your throat; swelling of your lips, tongue, or face; or hives); seizures; increased or irregular heartbeats; or severe nausea or vomiting.

Other, less serious side effects may also occur, although they are not common at appropriate doses. Continue to take aminophylline and talk to your doctor if you experience slight nausea, decreased appetite, or weight loss; restlessness, tremor, or insomnia; or headache, lightheadedness, or dizziness.

Side effects other than those listed here may also occur. Talk to your doctor about any side effect that seems unusual or that is especially bothersome

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.

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

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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 (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 Aminophylline 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

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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.

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6. Pharmaceutical particulars

6.1 List of excipients

Iso Propyl Alcohol

Croscarmellose Sodium

Silicon Dioxide

Talcum

Magnesium Stearate

Microcrystalline Cellulose (102 Grade)

Film coat FC Iron Oxide Red

Iso Propyl Alcohol

Methylene Chloride

6.2 Incompatibilities

There are no major incompatibilities.

6.3 Shelf life

36 Months.

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of container

AMINOPHYLLINE TABLETS BP 100 MG are available in Jar packs of 1000 Tablets.

6.6 Special precautions for disposal and other handling

None.