

AMINOPHYLLINE TABLETS BP

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1. Name of the medicinal product

Aminophylline Tablets BP.

2. Qualitative and quantitative composition

Each tablet contains aminophylline anhydrous 100 mg.

For the full list of excipients, see 6.1.

3. Pharmaceutical form

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

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

Dosing initiation and titration η [*Aminophylline equivalent in (*)]

η Patients with more rapid metabolism, clinically identified by higher than average dose requirements, should receive a smaller dose more frequently to prevent breakthrough symptoms resulting from low trough concentrations before the next dose. A reliably absorbed slow-release formulation will decrease fluctuations and permit longer dosing intervals.

A. Children (1-15 years) and adults (16-60 years) without risk factors for impaired clearance.

Titration Step Children < 45 kg Children > 45 kg and adults

1. Starting Dosage 12-14 (*15.2-17.7) mg/kg/day up to a maximum of 300 (*380)mg/day divided Q4-6 hrs η 300

(*380) divided Q6-8 hrs η 2. After 3 days, **if tolerated,**

increase dose to: 16 (*20.3) mg/kg/day up to a maximum of 400 (*507) mg/day divided Q4-6 hrs η 400 (*507) mg/day divided Q6-8 hrs η 3. After 3 more days, **if tolerated.**

increase dose to: 20 (*25.3) mg/kg/day up to a maximum of 600 mg (*760) mg/day divided Q4-6 hrs η 600 (*760) mg/day divided Q6-8 hrs η

B. Patients With Risk Factors For Impaired Clearance, The Elderly (>60 Years), And Those In Whom It Is Not Feasible To Monitor Serum Theophylline Concentrations:

In children 1-15 years of age, the final theophylline dose should not exceed 16 (*20.3) mg/kg/day up to a maximum of 400 (*507) mg/day in the presence of risk factors for reduced theophylline clearance (see **WARNINGS**) or if it is not feasible to monitor serum theophylline concentrations.

In adolescents ≥ 16 years and adults, including the elderly, the final theophylline dose should not exceed 400 (*507) mg/day in the presence of risk factors for reduced theophylline clearance (see **WARNINGS**) or if it is not feasible to monitor serum theophylline concentrations.

C. Loading Dose for Acute Bronchodilatation: An inhaled beta-2 selective agonist, alone or in combination with a systemically administered corticosteroid, is the most effective treatment for acute exacerbations of reversible airways obstruction. Theophylline is a relatively weak bronchodilator, is less effective than an inhaled beta-2 selective agonist and provides no added benefit in the treatment of acute bronchospasm. If an inhaled or parenteral beta agonist is not available, a loading dose of an oral immediate release theophylline can be used as a temporary measure. A single 5 mg/kg dose of theophylline, in a patient who has not received any theophylline in the previous 24 hours, will produce an average peak serum theophylline concentration of 10 mcg/mL (range 5-15 mcg/mL). If dosing with theophylline is to be continued beyond the loading dose, the guidelines in Sections A.3, or B., above, should be utilized and serum theophylline concentration monitored at 24 hour intervals to adjust final dosage.

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 theophylline 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 theophylline concentrations may be required in patients with hyperthyroidism (and when starting acute hyperthyroidism treatment) and cystic fibrosis.

Theophylline 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 theophylline 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 theophylline 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 theophylline.

The following reduce clearance of theophylline 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.

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

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

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

Theophylline 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 theophylline in pregnant women. Theophylline 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.

Theophylline should not be administered during pregnancy unless clearly necessary.

Breast-feeding

Theophylline 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

PHYLLOCONTIN CONTINUS 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 theophylline. 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
Skin and subcutaneous tissue disorders	Vomiting
	Pruritus
Renal and urinary disorders	Rash
	Diuresis
	Urinary retention*

* Please refer to section 4.4 as theophylline 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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Theophylline has a low therapeutic index. Theophylline 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 theophylline 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 theophylline 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: R03D A05

Aminophylline (theophylline) 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.

Theophylline 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 theophylline 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

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

Biotransformation

Theophylline is metabolised in the liver to 1, 3 dimethyluric acid, 1 methyluric acid and 3-methylxanthine.

Elimination

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

Factors affecting clearance

The predominant factors which alter theophylline 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 theophylline. However, oral theophylline administered daily to rats and mice for 2 years did not show carcinogenicity. Therefore, it is unlikely that theophylline poses a carcinogenic risk in man.

Reproductive and Developmental Toxicity

Theophylline 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 theophylline. Therefore theophylline should be considered to have the potential for developmental toxicity in man.

6. Pharmaceutical particulars

6.1 List of excipients

Maize Starch

Cetostearyl Alcohol

Purified Talc

Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

1000 Tablets Packed in a Amber Coloured HDPE PET Bottle .

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

SOLE AGENT : MACDECH PHARMA CO. LTD.

NAFDAC REG. NO. : B4-6947