

AUSTRALIAN PRODUCT INFORMATION – DBL™ AMINOPHYLLINE (Aminophylline) injection

1. NAME OF THE MEDICINE

Aminophylline

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 25 mg of aminophylline (equivalent to 20.63 mg of theophylline) in water for injections. The pH of the solution is between 8.8 and 10.0.

For the full list of excipients, see 6.1 List of excipients.

3. PHARMACEUTICAL FORM

DBL Aminophylline Injection 250 mg in 10 mL is a clear, colourless, sterile solution for injection, containing aminophylline (theophylline and ethylenediamine) in water for injections.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

DBL Aminophylline Injection is indicated for the treatment of reversible bronchospasm associated with chronic bronchitis, emphysema, bronchial asthma and chronic obstructive pulmonary disease. It may also be used for paroxysmal dyspnoea associated with left heart failure.

4.2 Dose and Method of Administration

Dosage

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.

A loading dose is generally administered over 20 to 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 to 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 (see Section 4.4 Special Warnings and Precautions for Use).

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.

Table 1 – Loading dose and maintenance dose of Aminophylline based on patient’s age or characteristics

Patients	Loading dose mg aminophylline/kg	Maintenance dose mg aminophylline/kg/hour	
		for next 12 h	beyond 12 h
Children 6 months to 9 yrs	6 (4.74)*	1.2 (0.95)*	1.0 (0.79)*
Children 9 to 16 yrs	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 pulmonale	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

Use in Elderly

DBL Aminophylline Injection should be administered with caution in elderly patients (see Section 4.4 Special Warnings and Precautions for Use).

Method of Administration

DBL Aminophylline Injection may be administered by intravenous infusion, or by slow intravenous injection at a rate not exceeding 20 to 25 mg/min.

4.3 Contraindications

DBL Aminophylline Injection is contraindicated in patients hypersensitive to xanthines or to ethylenediamine.

DBL Aminophylline Injection is also contraindicated in patients with coronary artery disease where myocardial stimulation might prove harmful.

DBL Aminophylline Injection is also contraindicated in patients with bronchiolitis (bronchopneumonia).

4.4 Special Warnings and Precautions for Use

When Signs or Symptoms of Theophylline Toxicity Are Present:

Whenever a patient receiving theophylline develops nausea or vomiting, particularly repetitive vomiting, or other signs or symptoms consistent with theophylline toxicity (even if another cause may be suspected), the intravenous infusion should be stopped and a serum theophylline concentration measured immediately.

General:

Prior to initiation of theophylline therapy or an increase in theophylline dose, careful consideration should be given to the various interacting drugs and physiologic conditions that can alter theophylline clearance and may require dosage adjustment.

Monitoring Serum Theophylline Concentrations:

Serum theophylline concentration measurements should be used to determine whether the dosage is appropriate and should be measured as follows:

1. Before making a dose increase to determine whether the serum concentration is subtherapeutic in a patient who continues to be symptomatic.
2. Whenever signs or symptoms of theophylline toxicity are present.
3. Whenever there is a new illness, worsening of an existing concurrent illness or a change in the patient's treatment regimen that may alter theophylline clearance (e.g. $>39^{\circ}\text{C}$ sustained for ≥ 24 hours, hepatitis, or drugs listed in Section 4.5 are added or discontinued).

In patients who have received no theophylline in the previous 24 hours, a serum concentration should be measured 30 minutes after completion of the intravenous loading dose to determine whether the serum concentration is <10 microgram/mL indicating the need for an additional loading dose or >20 microgram/mL indicating the need to delay starting the constant intravenous infusion. Once the infusion is begun, a second measurement should be obtained after one expected half-life (e.g. approximately 4 hours in children aged 1 to 9 years, and 8 hours in non-smoking adults). The second measurement should be compared to the first to determine the direction in which the serum concentration has changed. The infusion rate can then be adjusted before steady state is reached in an attempt to prevent an excessive or sub-therapeutic theophylline concentration from being achieved.

If a patient has received theophylline in the previous 24 hours, the serum concentration should be measured before administering an intravenous loading dose to make sure that it is safe to do so. If a loading dose is not indicated (i.e., the serum theophylline concentration is ≥ 10 microgram/mL), a second measurement should be obtained as above at the appropriate time after starting the intravenous infusion. If, on the other hand, a loading dose is indicated, a second blood sample should be obtained after the loading dose and a third sample should be obtained one expected half-life after starting the constant infusion to determine the direction in which the serum concentration has changed.

Once the above procedures related to initiation of intravenous theophylline infusion have been completed, subsequent serum samples for determination of theophylline concentration should be obtained at 24-hour intervals for the duration of the infusion. The theophylline infusion rate should be increased or decreased as appropriate based on the serum theophylline levels.

When signs or symptoms of theophylline toxicity are present, the intravenous infusion should be stopped and a serum sample for theophylline concentration should be obtained as soon as possible, analysed immediately, and the result reported to the clinician without delay. In patients in whom decreased serum protein binding is suspected (e.g., cirrhosis, women during the third trimester of pregnancy), the concentration of unbound theophylline should be measured and the dosage adjusted to achieve an unbound concentration of 6-12 microgram/mL.

Saliva concentrations of theophylline cannot be used reliably to adjust dosage without special techniques.

Conditions That Reduce Theophylline Clearance:

DBL Aminophylline Injection should be used with extreme caution in patients currently undergoing therapy with other xanthines, such as theophylline, as the hazard of serious toxicity is increased.

There are several readily identifiable causes of reduced theophylline clearance. **If the infusion rate is not appropriately reduced in the presence of these risk factors, severe and potentially fatal theophylline toxicity can occur.** Careful consideration must be given to the benefits and risks of theophylline use and more intensive monitoring of serum theophylline concentrations should always be obtained in these patients prior to any aminophylline administration since clearance may be decreased and hence toxicity may be more likely in these patients. DBL Aminophylline Injection should be used with caution in patients with the following risk factors:

- ***Smoking cessation***

- ***Age***
 - Neonates (term and premature)
 - Children <1 year
 - Elderly (>60 years)

- ***Concurrent Diseases***
 - Congestive heart failure
 - Chronic alcoholism,
 - Acute febrile illness (>39°C for 24 hours or more) or lesser temperature elevations for longer periods
 - Chronic obstructive pulmonary disease
 - Cor pulmonale
 - Influenza or those undergoing influenza immunisation
 - Renal dysfunction including reduced renal function in infants <3 months of age
 - Hepatic dysfunction, including hepatic cirrhosis, acute hepatitis
 - Hypothyroidism
 - Acute pulmonary oedema or pneumonia
 - Sepsis with multi-organ failure
 - Shock

DBL Aminophylline Injection may lower the seizure threshold and should be administered with caution in patients with seizure disorder unless the patient is receiving appropriate anticonvulsant therapy. Dose adjustment of any anticonvulsant medication may be required.

DBL Aminophylline Injection should be administered with caution in patients with the following clinical conditions due to the increased risk of exacerbation of the concurrent condition:

- Active peptic ulcer
- Seizure disorders
- Hyperthyroidism
- Hypertension
- Glaucoma
- Diabetes mellitus
- Cardiac arrhythmias (excluding bradyarrhythmias)
- Gastroesophageal reflux

Where myocardial stimulation would be harmful, DBL Aminophylline Injection should be administered with caution in patients with:

- Compromised cardiac or circulatory function
- Angina pectoris
- Acute myocardial injury

Intravenous aminophylline must be administered slowly and cautiously to prevent dangerous CNS or cardiovascular toxicity. Too rapid intravenous administration may result in the following symptoms: anxiety, headache, nausea and vomiting, severe hypotension, dizziness, faintness, light-headedness, palpitations, syncope, precordial pain, flushing, profound bradycardia, premature ventricular contractions, cardiac arrest.

Intramuscular administration is not recommended as it causes intense local pain and sloughing of tissue.

The coagulation time of the blood is shortened with aminophylline therapy.

Dosage Increases

Increases in the dose of intravenous theophylline should not be made in response to an acute exacerbation of symptoms unless the steady-state serum theophylline concentration is <10 microgram/mL (see also Section 4.2 Dose and Method of Administration).

As the rate of theophylline clearance may be dose-dependent (i.e. steady-state serum concentrations may increase disproportionately to the increase in dose), an increase in dose based upon a sub-therapeutic serum concentration measurement should be conservative. In general, limiting infusion rate increases to about 25% of the previous infusion rate will reduce the risk of unintended excessive increases in serum theophylline concentration.

Use in hepatic impairment

Theophylline clearance is decreased with hepatic (e.g. cirrhosis, acute hepatitis, cholestasis). Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in patients with reduced hepatic function.

Use in renal impairment

About 10% of the administered theophylline dose is excreted unchanged in the urine of adults. In contrast, approximately 50% of the administered theophylline dose is excreted unchanged in the urine of neonates. Therefore, careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in neonates with decreased renal function.

Use in the elderly

DBL Aminophylline Injection should be administered with caution. Elderly patients are at significantly greater risk of experiencing serious toxicity from theophylline than younger patients due to pharmacokinetic and pharmacodynamic changes associated with aging.

Theophylline clearance is reduced in patients greater than 60 years of age, resulting in increased serum theophylline concentrations in response to a given theophylline infusion rate. Protein binding may be decreased in the elderly resulting in a larger proportion of the total serum theophylline concentration in the pharmacologically active unbound form. Elderly patients also appear to be more sensitive to the toxic effects of theophylline after chronic overdosage than younger patients.

For these reasons, the maximum infusion rate of theophylline in patients greater than 60 years of age ordinarily should not exceed 17 mg/hr (21 mg/hr as aminophylline) unless the patient continues to be symptomatic and the peak steady state serum theophylline concentration is <10 microgram/mL. Theophylline infusion rates greater than 17 mg/hr (21 mg/hr as aminophylline) should be prescribed with caution in elderly patients.

Paediatric use

DBL Aminophylline Injection should be administered with caution in premature or neonatal infants and children <1 year.

The constant infusion rate of intravenous theophylline must be selected with caution in paediatric patients since the rate of theophylline clearance is highly variable across the age range of neonates to adolescents.

Due to the immaturity of theophylline metabolic pathways in paediatric patients under the age of one year, particular attention to dosage selection and frequent monitoring of serum theophylline concentrations are required when theophylline is prescribed to paediatric patients in this age group.

Children are particularly sensitive to xanthines, especially the CNS stimulant effects. The margin of safety above therapeutic doses is small. Rapid intravenous injection is not recommended in children.

Effects on Laboratory Tests

The Effect of Other Drugs on Theophylline Serum Concentration Measurements:

Most serum theophylline assays in clinical use are immunoassays which are specific for theophylline. Other xanthines such as caffeine, dyphylline and pentoxifylline are not detected by these assays. Some drugs (e.g. cefazolin, cephalothin), however, may interfere with certain HPLC techniques. Caffeine and xanthine metabolites in neonates or patients with renal dysfunction may cause the reading from some dry reagent office methods to be higher than the actual serum theophylline concentration.

Dipyridamole-assisted myocardial perfusion studies:

Aminophylline reverses the effects of dipyridamole on myocardial blood flow, thereby interfering with the test results. Dipyridamole-assisted myocardial perfusion studies should not be performed if therapy with aminophylline cannot be withheld for 36 hours prior to the test.

Uric acid serum determinations:

Aminophylline produces false-positive elevations of serum uric acid as measured by the Bittner or colorimetric methods, but not by the uricase method.

General

As a result of its pharmacological effects, theophylline at serum concentrations within the 10-20 microgram/mL range modestly increases plasma glucose (from a mean of 88 mg/dL to 98 mg/dL [4.9 mmol/L to 5.4 mmol/L]), uric acid (from a mean of 4 mg/dL to 6 mg/dL [0.24 mmol/L to 0.36 mmol/L]), free fatty acids (from a mean of 451 μ Eq/L to 800 μ Eq/L), total cholesterol (from a mean of 140 vs 160 mg/dL [3.6 vs 4.1 mmol/L]), HDL (from a mean of 36 to 50 mg/dL [0.9 to 1.3 mmol/L]), HDL/LDL ratio (from a mean of 0.5 to 0.7), and urinary free cortisol excretion (from a mean of 44 to 63 microgram/24 hr [121.4 to 173.9 nmol/24 hr]). Theophylline at serum concentrations within the 10–20 microgram/mL range may also transiently decrease serum concentrations of triiodothyronine (144 ng/dL [2.22 nmol/L] before, 131 ng/dL [2.02 nmol/L] after one week and 142 ng/dL [2.19 nmol/L] after 4 weeks of theophylline). The clinical importance of these changes should be weighed against the potential therapeutic benefit of theophylline in individual patients.

4.5 Interactions with Other Medicines and Other Forms of Interactions

Theophylline interacts with a wide variety of drugs. The interaction may be pharmacodynamic, i.e. alterations in the therapeutic response to theophylline or another drug or occurrence of adverse effects without a change in serum theophylline concentration. More frequently, however, the interaction is pharmacokinetic, i.e. the rate of theophylline clearance is altered by another drug resulting in increased or decreased serum theophylline concentrations.

The interactions listed in this section are not intended to be inclusive or comprehensive, Individual prescribing information from relevant drugs should be consulted.

The following drugs may inhibit theophylline metabolism and decrease aminophylline clearance resulting in increased serum levels and the potential for increased toxicity: alcohol, high dose allopurinol (> 600 mg/day), beta-blockers including propranolol, cimetidine, fluvoxamine, estrogen containing oral contraceptives, diltiazem, disulfuram, recombinant

alpha-interferon, methotrexate, mexiletine, tacrine, thiabendazole, thyroid hormones, ticlopidine, verapamil, pentoxifylline, and macrolide and quinolone antibiotics (including erythromycin, clarithromycin, ciprofloxacin, and enoxacin).

The following drugs may enhance theophylline metabolism and increase the clearance of aminophylline, and thereby decrease serum concentrations, possibly resulting in subtherapeutic dosing: aminoglutethimide, barbiturates including phenobarbital (phenobarbitone) and primidone, carbamazepine, isoprenaline, phenytoin, rifampicin, St John's wort (*Hypericum perforatum*), sulfinpyrazone, thioamines and tobacco and marijuana smoking.

If theophylline is being initiated in a patient who is already taking a drug that inhibits theophylline clearance (e.g. cimetidine, erythromycin), the dose of theophylline required to achieve a therapeutic serum theophylline concentration will be smaller. Conversely, if theophylline is being initiated in a patient who is already taking a drug that enhances theophylline clearance (e.g. rifampicin), the dose of theophylline required to achieve a therapeutic serum theophylline concentration will be larger. Discontinuation of a concomitant drug that increases theophylline clearance will result in accumulation of theophylline to potentially toxic levels, unless the theophylline dose is appropriately reduced. Discontinuation of a concomitant drug that inhibits theophylline clearance will result in decreased serum theophylline concentrations, unless the theophylline dose is appropriately increased.

In addition, the following drugs may interact with aminophylline:

Adenosine

Aminophylline may antagonise the cardiovascular effects of adenosine.

Beta-agonists

Concurrent use of aminophylline and beta-agonists may produce increased cardiotoxic effects. Also, aminophylline may potentiate the hypoglycaemia which may be associated with administration of beta-agonists.

Beta-blocking agents (including ophthalmic agents)

Concurrent use of aminophylline and beta-blockers may result in an inhibition of the bronchodilatory effects of aminophylline.

Benzodiazepines

Concurrent use of aminophylline and benzodiazepines may result in a reduction or reversal of the sedative effects of benzodiazepines.

Cardiac glycosides

Aminophylline may enhance the sensitivity of the myocardium to, and the toxic potential of, cardiac glycosides.

Ephedrine and other sympathomimetic amines

Concurrent use of aminophylline and sympathomimetic amines may result in increased nausea, nervousness or insomnia.

Halothane

Concurrent use of aminophylline and halothane may result in ventricular arrhythmias.

Ketamine

Concurrent use of aminophylline and ketamine may result in a lowered seizure threshold.

Lithium

Concurrent use of aminophylline and lithium may result in increased excretion of lithium, and hence a reduction in the therapeutic effect of lithium. Adjustment of the lithium dosage may be required.

Neuromuscular blocking agents, non-depolarising

Aminophylline may antagonise the neuromuscular blocking effects of these agents.

Xanthines

Concurrent use of aminophylline and other xanthine containing medications may result in additive toxicity and should be avoided (see Section 4.3 Contraindications).

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

No data available

Use in pregnancy – Category A

Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

The pharmacokinetics of aminophylline may be altered during pregnancy, and therefore serum theophylline concentrations may need to be measured more frequently in patients undergoing aminophylline therapy during pregnancy.

Use in lactation

Aminophylline, as theophylline, is distributed into breast milk, and may occasionally induce irritability or other signs of toxicity in the breast fed infants of mothers undergoing aminophylline therapy.

4.7 Effects on Ability to Drive and Use Machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse Effects (Undesirable Effects)

Adverse reactions associated with theophylline are generally mild when peak serum theophylline concentrations are <20 microgram/mL and mainly consist of transient caffeine-like adverse effects such as nausea, vomiting, headache, and insomnia. When peak serum

theophylline concentrations exceed 20 microgram/mL, however, theophylline produces a wide range of adverse reactions including persistent vomiting, cardiac arrhythmias, and intractable seizures which can be lethal (see Section 4.9 Overdose).

Other adverse reactions that have been reported at serum theophylline concentrations <20 microgram/mL include diarrhoea, irritability, restlessness, fine skeletal muscle tremors, and transient diuresis. In patients with hypoxia secondary to COPD, multifocal atrial tachycardia and flutter have been reported at serum theophylline concentrations ≥ 15 microgram/mL. There have been a few isolated reports of seizures at serum theophylline concentrations <20 microgram/mL in patients with an underlying neurological disease or in elderly patients. The occurrence of seizures in elderly patients with serum theophylline concentrations <20 microgram/mL may be secondary to decreased protein binding resulting in a larger proportion of the total serum theophylline concentration in the pharmacologically active unbound form. The clinical characteristics of the seizures reported in patients with serum theophylline concentrations <20 microgram/mL have generally been milder than seizures associated with excessive serum theophylline concentrations resulting from an overdose (i.e. they have generally been transient, often stopped without anticonvulsant therapy, and did not result in neurological residua).

Products containing aminophylline may rarely produce severe allergic reactions of the skin, including exfoliative dermatitis, after systemic administration in a patient who has been previously sensitised by topical application of a substance containing ethylenediamine. In such patients, skin patch tests are positive for ethylenediamine, a component of aminophylline, and negative for theophylline. Pharmacists and other individuals who experience repeated skin exposure while physically handling aminophylline may develop a contact dermatitis due to the ethylenediamine component.

Adverse reactions related to aminophylline administration

Cardiovascular system: tachycardia, palpitations, extrasystoles, increased pulse rate, flushing, hypotension, circulatory failure, atrial and ventricular arrhythmia, peripheral vasoconstriction.

Central nervous system: headache, nervousness, insomnia, irritability, restlessness, dizziness, reflex hyperexcitability, seizures, anxiety, tremor, lightheadedness, excitement.

Gastrointestinal system: nausea, vomiting, heartburn, epigastric pain, abdominal cramps, anorexia, diarrhoea, haematemesis.

Genitourinary: increased urination, albuminuria.

Other: fever.

Respiratory system: tachypnoea.

Skin and appendages: ethylenediamine hypersensitivity induced dermatitis (hives, skin rash, sloughing of skin).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

The chronicity and pattern of theophylline overdosage significantly influences clinical manifestations of toxicity, management and outcome. There are two common presentations:

- 1) acute overdose, i.e. infusion of an excessive loading dose or excessive maintenance infusion rate for less than 24 hours, and
- 2) chronic overdosage, i.e. excessive maintenance infusion rate for greater than 24 hours.

Clinical features

Less severe toxicities do not always precede major toxicities. Chronic overdose may produce toxicity at serum levels lower than those in acute overdose. In general, patients who experience an acute overdose are less likely to experience severe toxicity than patients who have experienced a chronic overdosage, unless the peak serum theophylline concentration is >90-100 microgram/mL. After a chronic overdosage, generalised seizures, life-threatening cardiac arrhythmias, and death may occur at serum theophylline concentrations >30 microgram/mL. The following signs and symptoms may be present in aminophylline overdose:

- **cardiovascular:** tachycardia, arrhythmias, palpitations, hypotension.
- **central nervous system:** agitation, confusion or altered behaviour including toxic psychosis, seizures.
- **gastrointestinal:** nausea, vomiting, diarrhoea and/or hematemesis, continuing or severe abdominal pain, acute pancreatitis.
- **genitourinary:** renal failure.
- **metabolic:** hyperglycaemia, hypokalaemia, metabolic acidosis, hypophosphataemia, hypercalcaemia.
- **respiratory:** tachypnoea, respiratory arrest, respiratory alkalosis.
- **other:** extreme thirst, slight fever, tinnitus.

The severity of toxicity after chronic overdosage is more strongly correlated with the patient's age than the peak serum theophylline concentration; patients >60 years are at the greatest risk for severe toxicity and mortality after a chronic overdosage. Pre-existing or concurrent disease may also significantly increase the susceptibility of a patient to a particular toxic manifestation, e.g. patients with neurologic disorders have an increased risk of seizures and patients with cardiac disease have an increased risk of cardiac arrhythmias for a given serum theophylline concentration compared to patients without the underlying disease.

Other manifestations of theophylline toxicity include increases in serum calcium, creatine kinase, myoglobin and leukocyte count, decreases in serum phosphate and magnesium, acute myocardial infarction, and urinary retention in men with obstructive uropathy.

Seizures associated with serum theophylline concentrations >30 microgram/mL are often resistant to anticonvulsant therapy and may result in irreversible brain injury if not rapidly controlled. Death from theophylline toxicity is most often secondary to cardio-respiratory arrest and/or hypoxic encephalopathy following prolonged generalised seizures or intractable cardiac arrhythmias causing haemodynamic compromise.

Treatment

There is no specific antidote for aminophylline overdose. Treatment of overdose is symptomatic and supportive. Administration of sympathomimetic drugs should be avoided. Treatment may involve the following measures:

- administration of oral activated charcoal, regardless of the route of exposure to aminophylline (this assists in decreasing the serum concentration of theophylline by interrupting the enterohepatic circulation). Oral activated charcoal should be repeated until the serum theophylline concentration is below 20 microgram/mL.
- charcoal hemoperfusion to increase the elimination of aminophylline. Hemodialysis is less effective in eliminating aminophylline, but may be warranted in some patients.
- administration of intravenous diazepam to control seizures. Where diazepam is ineffective, phenytoin, phenobarbital (phenobarbitone), or thiopentone may be considered.
- correction of fluid and electrolyte balance.
- support of respiratory functions by airway management, oxygen administration or mechanical ventilation as required.
- support of cardiac functions. Propranolol may be warranted in the presence of extreme tachycardia, and antiarrhythmic therapy may be required.
- administration of phenothiazines in the presence of life threatening hypothermia.
- monitoring of serum theophylline concentrations and ECG.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of action

Aminophylline is a 2:1 complex of theophylline and ethylenediamine. Aminophylline has greater water solubility than theophylline. In biological fluids aminophylline dissociates to theophylline hence the pharmacological effects of aminophylline are those of theophylline. Theophylline is a xanthine derivative with the main pharmacological action of direct relaxation of bronchial smooth muscle, relieving bronchospasm. The bronchodilatory effect of theophylline is minimal if bronchospasm is not the cause. The bronchodilatory effect may be via inhibition of selected phosphodiesterases, which produces an increase in intracellular cyclic AMP. Theophylline also directly stimulates the medullary respiratory centre. Other pharmacological effects of theophylline include stimulation of cardiac muscle (increasing both heart rate and myocardial contractility at higher doses), stimulation of the central nervous system, transient diuresis, increased gastric secretion, decreased peripheral resistance and cerebral vasoconstriction.

Clinical trials

No data available

Serum Concentration-Effect Relationship:

Theophylline, (and hence aminophylline), has a low therapeutic index. Serum theophylline concentrations of around 5 to 20 microgram/mL (27.5 to 110 micromole/L) are generally considered therapeutic. Serum theophylline concentrations greater than 20 microgram/mL (110 micromoles/L) are often associated with adverse reactions.

5.2 Pharmacokinetic Properties

The pharmacokinetics of theophylline vary widely among individuals due to differences in age, body weight, diet, smoking habits, certain concurrent illnesses and co-administration of other drugs that can significantly alter the pharmacokinetics of theophylline. Within-subject variability in metabolism has also been reported in some studies, especially in acutely ill patients. Thus, monitoring of serum theophylline concentrations is recommended (see Section 4.4, Special Warnings and Precautions for Use, Monitoring Serum Theophylline Concentrations)

Absorption

Aminophylline dissociates rapidly to theophylline in biological fluids.

Distribution

Theophylline is rapidly distributed throughout non-adipose tissues and extracellular fluids. Theophylline crosses the placenta, and is distributed into breast milk. The concentration of theophylline in breast milk is approximately 70% that found in the serum. The apparent volume of distribution of theophylline is 0.3 to 0.7 L/kg (average 0.45 L/kg).

Approximately 60% of theophylline in adults and 35% in premature infants and neonates is bound to plasma proteins.

Metabolism

Theophylline undergoes hepatic metabolism via the cytochrome P450 system. In adults the main metabolites are 1,3-dimethyl uric acid, 1-methyl uric acid, and 3-methylxanthine. The metabolism of theophylline has been reported to be capacity limited in some individuals, resulting in non-linear pharmacokinetics.

Excretion

Theophylline and its metabolites undergo renal excretion.

There is significant interpatient variability in the pharmacokinetics of theophylline, and hence aminophylline.

The serum half life of theophylline in otherwise healthy, non-smoking, asthmatic adults averages 7 to 9 hours, and theophylline clearance in this group is reported to be approximately 0.65 mL/kg/hr. Serum half life is increased and clearance decreased in the elderly and in patients with congestive heart failure, chronic obstructive pulmonary disease, cor pulmonale or liver disease. Serum half life is decreased and clearance increased in cigarette or marijuana smokers. Clearance in premature infants and neonates is reduced. Theophylline clearance increases during the first year of life and remains relatively constant during the first 9 years, then gradually declines to adult values by 16 years of age.

5.3 Preclinical Safety Data

Genotoxicity

No data available

Carcinogenicity

No data available

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Water for injections

6.2 Incompatibilities

Aminophylline precipitates in acidic media, but this does not apply to the dilute solutions in intravenous infusion fluids.

Aminophylline containing solutions are alkaline, and hence drugs known to be alkali labile should not be added to aminophylline containing solutions.

Aminophylline injection should not be mixed in a syringe with other drugs but should be added separately to the intravenous solution. When an intravenous solution containing aminophylline is given “piggyback”, the intravenous system already in place should be turned off while the aminophylline is infused if there is a potential problem with admixture incompatibility.

Aminophylline is reported to be incompatible with the following drugs:

Adrenaline (epinephrine) HCl, amiodarone, ascorbic acid, benzylpenicillin, chlorpromazine hydrochloride, ciprofloxacin, clindamycin, codeine phosphate, diltiazem, dimenhydrinate, dobutamine, doxapram, erythromycin gluceptate, hydralazine, hydroxyzine HCl, insulin, isoprenaline HCl, methadone HCl, methicillin sodium, morphine sulfate, noradrenaline (norepinephrine) acid tartrate monohydrate, oxytetracycline hydrochloride, pentazocine lactate, pethidine HCl, phenobarbital (phenobarbitone) sodium, phenytoin sodium, potassium, prochlorperazine edisylate, promazine hydrochloride, promethazine hydrochloride, ondansetron, tetracycline hydrochloride, vancomycin hydrochloride, vitamin B complex with C.

It is suggested that specialised literature be consulted before preparing admixtures with aminophylline and other drugs.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer unless solution is clear and container is undamaged. Discard unused portion. Do not use if crystals have separated from solution.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special Precautions for Storage

Store below 25°C. Protect from light.

6.5 Nature and Contents of Container

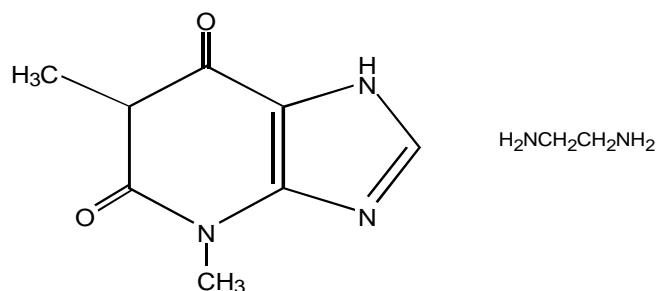
Strength	Pack size
250 mg in 10 mL	5 x 10 mL ampoules
250 mg in 10 mL	50 x 10 mL ampoules

6.6 Special Precautions for Disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical Properties

Chemical structure



The molecular formula of aminophylline is $(C_7H_8N_4O_2)_2 \cdot C_2H_4(NH_2)_2$. Its molecular weight is 420.4.

CAS number

The CAS Registry number of anhydrous aminophylline is 317-34-0.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
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9. DATE OF FIRST APPROVAL

19 May 1998

10. DATE OF REVISION

01 August 2023

Summary Table of Changes

Section changed	Summary of new information
All	Minor editorial updates
4.2	Heading added to direct reader elsewhere to information on use in the elderly.
4.4	Information added regarding: <ul style="list-style-type: none">- General precautions- Monitoring serum theophylline concentrations- How to increase dose safely- Use in hepatic impairment- Use in renal impairment- Additional information for use in the elderly- Effects in laboratory tests
4.5	Additional guidance provided relating to interactions
4.8	Adverse reactions based on peak serum theophylline concentrations included
4.9	Information regarding overdose refined, with an introductory paragraph added, as well as additional manifestations of overdose.
5.2	Introductory pharmacokinetic information added Additional metabolism clarification included.