

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Aminophylline Injection BP

250 mg/10 mL

Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sterile solution of aminophylline (theophylline and ethylenediamine). Each mL contains 25 mg of aminophylline (equivalent to 20.63 mg of theophylline).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

DBL™ Aminophylline Injection 250 mg in 10 mL is a clear, colourless, solution for injection.

The pH of the solution is between 8.8 and 10.0.

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

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

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. 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/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 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

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

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. A serum theophylline concentration should always be obtained in these patients prior to any aminophylline administration.

DBL™ Aminophylline Injection should be used with caution in:

- elderly patients,
- premature or neonatal infants,
- patients with congestive heart failure,
- chronic alcoholism,
- acute febrile illness,
- chronic obstructive pulmonary disease,
- cor pulmonale,
- influenza or those undergoing influenza immunization,
- renal or hepatic dysfunction, including hepatic cirrhosis,
- hypothyroidism,
- acute pulmonary oedema or pneumonia,

since clearance may be decreased and hence toxicity may be more likely in these patients.

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:

- peptic ulcer,
- hyperthyroidism,
- hypertension,
- glaucoma,
- diabetes mellitus,
- tachyarrhythmia,
- gastroesophageal reflux,

since these conditions may be exacerbated.

DBL™ Aminophylline Injection should be administered with caution in patients with:

- compromised cardiac or circulatory function,
- angina pectoris or

- acute myocardial injury,

where myocardial stimulation would be harmful.

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, lightheadedness, 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.

Laboratory interactions

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.

Paediatric population

Children are particularly sensitive to xanthines, especially the CNS stimulant effects. The margin of safety above therapeutic doses is small. Consequently, serum theophylline levels should be carefully monitored in paediatric patients. Rapid intravenous injection is not recommended in children.

4.5 Interaction with other medicines and other forms of interaction

The following drugs may decrease aminophylline clearance resulting in increased serum levels and the potential for increased toxicity: alcohol, high dose allopurinol (> 600 mg/day), beta-blockers, cimetidine, oestrogen containing oral contraceptives, diltiazem, disulfuram, recombinant alpha-interferon, methotrexate, mexiletine, propranolol, tacrine, thiabendazole, thyroid hormones, ticlopidine, verapamil, and macrolide antibiotics and quinolones (including erythromycin, clarithromycin, ciprofloxacin and enoxacin).

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

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-depolarizing

Aminophylline may antagonize 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).

4.6 Fertility, pregnancy and lactation

Pregnancy

Category A. This category includes 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 foetus 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.

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.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

No data available.

4.8 Undesirable effects

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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

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. Potentially life threatening toxicities may occur at serum concentration greater than 40 microgram/mL (220 micromole/L) in chronic overdose. In acute overdose serum concentrations greater than 90 microgram/mL (495 micromole/L) are generally associated with severe toxicity.

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:** tachypnea, respiratory arrest, respiratory alkalosis.
- **other:** extreme thirst, slight fever, tinnitus.

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, 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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.

5.2 Pharmacokinetic properties

Aminophylline dissociates rapidly to theophylline in biological fluids. 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.

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. 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.

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.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

Reproductive and developmental toxicity

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 is reported to be incompatible with the following drugs: adrenaline, amiodarone, ascorbic acid, benzylpenicillin, chlorpromazine hydrochloride, ciprofloxacin, clindamycin, codeine phosphate, diltiazem, dimenhydrinate, dobutamine, doxapram, erythromycin gluceptate, hydralazine, hydroxyzine HCl, insulin, methadone HCl, methicillin sodium, morphine sulfate, noradrenaline acid tartrate, oxytetracycline hydrochloride, pentazocine lactate, pethidine HCl, phenobarbitone sodium, phenytoin sodium, potassium, prochlorperazine edisylate, promazine hydrochloride, promethazine hydrochloride, ondansetron, tetracycline hydrochloride, vancomycin hydrochloride, vitamin B complex with C.

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

6.3 Shelf life

30 months.

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, glass
250 mg in 10 mL	50 x 10 mL ampoules, glass

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand
Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

09 July 1981

10. DATE OF REVISION OF THE TEXT

11 February 2019

Summary table of changes

Section changed	Summary of new information
All	New Data Sheet format in accordance with Medsafe guidance.