

Product Summary

1. Trade Name of the Medicinal Product

Aminophylline Injection B.P. 250mg/10ml.

2. Qualitative and Quantitative Composition

Each 10ml of solution contains aminophylline hydrate B.P. 250mg.

3. Pharmaceutical Form

Clear, sterile solution for injection, intended for parenteral administration to human beings.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aminophylline is a complex of theophylline and ethylenediamine and is given for its theophylline activity to relax smooth muscle and to relieve bronchial spasm.

Aminophylline Injection is indicated for relief of bronchospasm associated with asthma and in chronic obstructive pulmonary disease.

4.2 Posology and method of administration

Aminophylline Injection B.P. 250mg/10ml is for slow intravenous administration. The solution may be injected very slowly, or it may be infused in a small volume of either 5% dextrose or 0.9% sodium chloride injection.

Maintenance therapy can be administered via larger volume infusion solutions, rate-regulated to deliver the required amount of drug each hour.

Therapeutic plasma concentrations of theophylline are considered to be in the range of 5 to 20mcg/ml and levels above 20mcg/ml are more likely to be associated with toxic effects. There is marked interpatient variation in the dosage required to achieve plasma levels of theophylline that are within the desired therapeutic range.

During therapy, patients should be monitored carefully for signs of toxicity and, where possible, the serum theophylline levels should also be monitored.

In the following dosage guidelines for the intravenous administration of aminophylline, doses should be calculated on the basis of lean (ideal) body weight; the drug is not recommended for infants under 6 months of age due to the marked variation in theophylline metabolism in infants;

1. PATIENTS NOT ALREADY RECEIVING THEOPHYLLINE PRODUCTS

- (a) A loading dose of 6mg/kg body weight of aminophylline may be given by slow intravenous injection at a rate not exceeding 25mg/min.
- (b) Depending on the status of the patient, the maintenance dose for the next 12 hours may be considered as follows:

Children aged 6 months to 9 years:	1 .2mg/kg/hour (reducing to 1mg/kg/hour beyond 12 hours).
Children aged 9 years to 16 years and young adult smokers:	1mg/kg/hour (reducing to 0.8mg/kg/hour beyond 12 hours).
Otherwise healthy non-smoking adults:	0.7mg/kg/hour (reducing to 0.5mg/kg/hour beyond 12 hours).
Older patients and those with cor pulmonale:	0.6mg/kg/hour (reducing to 0.3mg/kg/hour beyond 12 hours).
Patients with congestive cardiac failure or hepatic disease:	0.5mg/kg/hour (reducing to 0.1 - 0.2mg/kg/hour beyond 12 hours).

2. PATIENTS ALREADY RECEIVING THEOPHYLLINE PRODUCTS

The loading dose should be adjusted on the basis that each 0.5mg/kg of theophylline administered as a loading dose will result in a 1 mcg/ml increase in serum theophylline concentration.

Ideally, the loading dose should be deferred until serum theophylline levels can be determined. If this is not possible and if the clinical situation requires that the drug be administered, a dose of 3.1 mg/kg of aminophylline (equivalent to 2.5mg/kg of anhydrous theophylline) may be considered on the basis that it is likely to increase the serum theophylline concentration by approximately 5mcg/ml when administered as a loading dose.

Subsequently, the maintenance dosage recommendations are the same as those described above.

4.3 Contraindications

Aminophylline should not be administered to patients with a known hypersensitivity to the xanthine group of drugs.

4.4 Special warnings and precautions for use

Elderly patients, or those with cardiac or hepatic disease should be monitored carefully for signs of theophylline toxicity. Children are particularly susceptible to the effects of theophylline and care is required when administering aminophylline to children.

There have been reports of seizures in children with theophylline plasma levels within the accepted therapeutic range. Alternative treatment should be considered in patients with a history of seizure activity and, if Aminophylline Injection is used in such patients, they should be carefully observed for possible signs of central stimulation.

Because the mean half-life of theophylline is shorter in smokers than in non-smokers, the former group may require larger doses of aminophylline.

To reduce the undesirable stimulating effects of aminophylline on the central nervous and cardiovascular systems, intravenous administration of the drug should be slow and should not exceed a rate of 25 mg/min.

Methylxanthines may increase gastric acidity and care should be taken when they are used in patients with a history of peptic ulceration.

Aminophylline should not be administered concurrently with other xanthine medications.

The label shall contain the following statements:-

Protect from light.

Store below 25°C.

If only part used discard the remaining solution.

Discard the ampoule if the contents are discoloured.

4.5 Interactions with other medicinal products and other forms of interaction

Increased serum levels of theophylline have been reported in patients who were also taking cimetidine, erythromycin, ciprofloxacin, allopurinol, thiabendazole, diltiazem or oral contraceptives. Factors such as viral infection or cardiac failure can also reduce theophylline clearance. There is an increased likelihood of toxicity occurring if ephedrine or other sympathomimetic agents are given concomitantly with aminophylline.

The concomitant use of theophylline and fluvoxamine should usually be avoided. Where this is not possible, patients should have their theophylline dose halved and plasma theophylline should be monitored closely. Factors such as cardiac failure or viral infection, including infection with influenza virus, can also reduce theophylline clearance.

Smoking can increase clearance of theophylline, as can carbamazepine, phenytoin, rifampicin and sulphapyrazone.

Xanthines can potentiate hypokalaemia resulting from beta₂ agonist therapy, steroids, diuretics and hypoxia. Particular caution is advised in severe asthma. It is recommended that serum potassium levels are monitored in such situations.

4.6 Pregnancy and lactation

As with other drugs, aminophylline should only be used during pregnancy if considered essential by the physician. Theophylline crosses the placenta and is secreted into breast milk.

4.7 Effects on ability to drive and use machines

None Stated.

4.8 Undesirable effects

Aminophylline may cause gastro-intestinal irritation, with nausea, vomiting and abdominal pain. Symptoms of central nervous system stimulation may occur, including insomnia, restlessness and anxiety. Theophylline can precipitate cardiac arrhythmias and hypotension may follow intravenous injection, particularly if the injection is too rapid. Allergic reactions to aminophylline may occur.

4.9 Overdose

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 sustained release formulations.

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

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

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

Metabolic features: 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.

Pharmacological Properties

5.1 Pharmacodynamic Properties

Aminophylline is a complex of theophylline and ethylenediamine and is given for its theophylline activity to relax smooth muscle and to relieve bronchial spasm. Theophylline is a smooth muscle relaxant and it relaxes the smooth muscle of the bronchial airways. Other actions of theophylline include cardiac stimulation, CNS stimulation, decreased peripheral vascular resistance and diuresis.

5.2 Pharmacokinetic Properties

Theophylline is approximately 60% bound to plasma proteins but binding is decreased to about 40% in neonates and in adults with hepatic disease. The drug is widely distributed and it crosses the placenta and passes into breast milk.

Theophylline is metabolised in the liver and the metabolites are excreted in the urine. In adults, about 10% of a dose of theophylline is excreted unchanged in the urine. There is considerable inter-individual variation in the rate of hepatic metabolism of theophylline, resulting in large variations in clearance, serum concentrations and half-lives. Cigarette smoking increases theophylline clearance and shortens its serum half-life.

5.3 Preclinical Safety Data

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Ethylenediamine Hydrate B.P.
Water for Injections B.P.

6.2. Incompatibilities

Incompatibility has been reported with chlorpromazine, clindamycin, corticotrophin, dimenhydrinate, doxorubicin, erythromycin gluceptate, hydralazine hydrochloride, hydroxyzine hydrochloride, opioid analgesics, oxytetracycline hydrochloride, phenytoin sodium, procaine hydrochloride, prochlorperazine salts, promazine hydrochloride, promethazine hydrochloride, sulphafurazole diethanolamine and vancomycin hydrochloride.

6.3. Shelf Life

Unopened : 3 years (36 months).

After reconstitution : not applicable.

After first opening : not applicable*.

* If only part of an ampoule is used, discard the remaining solution.

6.4. Special Precautions for Storage

Do not store above 25°C

Keep in outer carton

6.5. Nature and Contents of Container

10 ml, clear glass ampoules, glass type 1 Ph.Eur. borosilicate glass presented in cardboard cartons to contain 10 x 10 ml ampoules.

6.6. Instruction for Use/Handling

For slow intravenous injection.

Use as directed by the physician.

Keep out of reach of children.

If only part used, discard the remaining solution.

Discard the ampoule if the contents are discoloured.

7. MARKETING AUTHORISATION HOLDER

Antigen International Ltd.,
Roscrea,
Co. Tipperary,
Ireland.

8. MARKETING AUTHORISATION NUMBER

PL 2848/5910R.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date granted: 25 November 1986.

Date renewed: 23 June 1992.

10. DATE OF REVISION OF THE TEXT

July 2004