

Part II

Summary of Product Characteristics

1) Name of the medicinal product

Aminophylline Injection BP 250mg in 10ml (25mg in 1ml)

2) Qualitative and Quantitative composition

Each 10ml of solution contains 250mg of Aminophylline Hydrate equivalent to 239.73mg of Aminophylline.

3) Pharmaceutical form

Solution for Injection
A clear colourless solution.

4) Clinical Particulars

4.1 Therapeutic Indications

In the management of bronchospasm, e.g. in asthma, chronic bronchitis and emphysema.

4.2 Posology and method of administration

Aminophylline Injection BP 250mg in 10ml is for slow intravenous administration at a rate not exceeding 25mg per minute.

Therapeutic plasma concentrations of theophylline should be maintained in the range of 10 to 20mcg/ml and levels above 20mcg/ml are more likely to be associated with toxic effects. There is a 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 (see precautions and warnings below)

Loading Dose:

Adults:

For patients not currently receiving Xanthine therapy an initial dose of 6mg aminophylline/kg should be given at a rate not exceeding 25mg/minute (containing 20mg/minute theophylline). Loading doses are usually given over 20 to 30 minutes.

For patients already receiving Xanthine therapy the loading dose must be reduced to avoid overdosage. Ideally, the serum theophylline concentration should be obtained and a loading dose given based on the principle that each 0.5mg/kg administered will result in a 1mcg/ml increase in the serum concentration of theophylline. Where the serum level cannot be determined and there is urgent clinical need, 3.1mg aminophylline/kg (2.5mg theophylline/kg) should be given slowly: this will increase the serum level by about 5mcg/ml.

For optimum therapeutic effect and to avoid undue risk of side effects, the serum level should be maintained in the range 10 to 20mcg/ml.

Children:

For children of 1 to 9 years who are not currently receiving xanthine therapy, a loading dose of 3 to 6mg/kg may be given over 30 minutes.

Maintenance dosage:

The following table gives guidance for maintenance dosage.

This applies to all patients.

	Maintenance dosage	
	First 12 hours (mg/kg/hr)	Beyond 12 hours (mg/kg/hr)
Children 1-9 years	0.9	
Children 9-16 and young adult smokers	1.0	0.8
Otherwise healthy non-smoking adults	0.7	0.5
Elderly patients	0.6	0.3
Patients with congestive heart failure, liver failure	0.5	0.1 – 0.2

4.3 Contraindications

Use in patients with a known hypersensitivity to the xanthine group of drugs.

4.4 Special Warnings and precautions for use

Caution should be exercised when used in elderly patients and patients with cardiac disease.

In patients with impaired hepatic or renal function, viral infections and cardiac failure, the half life of theophylline may be longer than usual. In such patients the dosage should be reduced and serum levels carefully monitored.

Patients with a history of peptic ulcer may suffer an exacerbation when receiving aminophylline.

Monitoring of serum levels is recommended; serum theophylline values should be maintained in the range of 10 to 20 mcg/ml.

In order to assess the dosage of the intravenous infusion; serum theophylline measurements should be ideally carried out thirty minutes and twelve hours after commencement of the IV infusion.

Herbal preparations containing St. John's wort (*Hypericum perforatum*) should not be used while taking Aminophylline injection due to the risk of decreased plasma concentrations and reduced clinical effects of Aminophylline Injection (see 4.5 Interactions).

There have been reports of seizures with 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.

4.5 Interaction with other medicinal products and other forms of interaction

The effect of aminophylline may be potentiated by concomitant treatment with ciprofloxacin, cimetidine, erythromycin, allopurinol, thiabendazole, diltiazem and oral contraceptives.

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.

Plasma concentrations of theophylline may be reduced following treatment with carbamazepine, phenytoin, rifampicin, barbiturates and sulphapyrazone.

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

Plasma concentrations of theophylline can be reduced by concomitant use of the herbal preparation St. John's wort (*Hypericum perforatum*). This is due to the induction of drug metabolizing enzymes by St. John's wort. Herbal preparations containing St. John's wort should therefore not be combined with Aminophylline injection. The inducing effect may persist for at least after cessation of treatment with St. John's wort. If a patient is already taking St. John's wort, check theophylline levels and stop St. John's wort. Theophylline may increase on stopping St. John's wort. The dose of theophylline may require adjusting.

Factors like cardiac failure and viral infection can also reduce theophylline clearance. There is an increased likelihood of toxicity occurring if ephedrine or other sympathomimetic agents are given concomitantly with Aminophylline.

Care should be taken in its concomitant use with beta-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.

The effect of aminophylline may be potentiated by concomitant administration with fluoroquinones and fluvoxamine.

4.6 Pregnancy and lactation

This product should not be administered during pregnancy and lactation unless considered essential by physician. Theophylline crosses the placenta and it enters breast milk. Safety in pregnancy has not been established.

4.7 Effects on the ability to drive and use machines

Nil

4.8 Undesirable effects

Aminophylline may cause gastro-intestinal irritation, with nausea, vomiting and abdominal pain. Symptoms of central nervous system may occur, including insomnia, restlessness and anxiety. Allergic reaction 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.

There is no specific antidote and treatment is symptomatic and supportive. Metabolic abnormalities, especially hypokalaemia, should be corrected and convulsions controlled by intravenous administration of diazepam. Theophylline is dialyzable: charcoal haemoperfusion and haemodialysis should be considered in cases of severe toxicity.

Serial plasma theophylline should be measured until a decreasing trend to levels below 20mcg/ml has been demonstrated.

5 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 spasm. Theophylline competitively inhibits phosphodiesterase with a resultant increase in intracellular concentrations of cyclic AMP. Theophylline is a smooth muscle relaxant and it relaxes smooth muscles of bronchial airways. Other action 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 40% in neonates and in adults with hepatic diseases. The drug is widely distributed and it crosses the placenta and passes into breast milk. Theophylline is metabolized in the liver and the metabolites are excreted in the urine.

There is a 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. The serum half-life of Theophylline in an otherwise healthy, non-smoking asthmatic adult is 7 to 9 hours; shorter half-lives are found in children and in cigarette smokers.

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
Water for injections

6.2 Incompatibilities

Solutions of aminophylline are alkaline and if the pH falls below 8, crystals of Theophylline will deposit. Drugs known to be unstable in alkaline solutions should not be mixed with aminophylline nor should drugs that could lower the pH below the critical value.

6.3 Shelf life

Unopened: 3 years
The product should be used immediately after opening.

6.4 Special precautions for storage

Do not store above 25°C.
Keep ampoules in outer carton.

6.5 Nature and contents of the container

10ml, clear glass ampoules, glass type I Ph. Eur. Borosilicate glass packed in cardboard cartons to contain 10 x 10ml ampoules.

6.6 Instructions for use and handling

For single use only.

Discard the ampoules if the contents are discoloured.

In only part of the contents of an ampoule is used, the remaining solution should be discarded.

7 Marketing Authorisation Holder

Antigen Pharmaceuticals Ltd
Roscrea
County Tipperary.

8 Marketing authorization Number

PA 73/99/1

9 Date of First authorization/Renewal of Authorisation

Date of first authorization: 1st September 1988

Date of last renewal: 1st September 2003

10 Date of revision of the text

September 2008.