



## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **PRODUCT SUMMARY**

#### **1. NAME OF THE MEDICINAL PRODUCT**

Aminophylline Injection BP

#### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each ml contains 25mg of Aminophylline Ph Eur

#### **3. PHARMACEUTICAL FORM**

Sterile Injection

#### **4. CLINICAL PARTICULARS**

##### **4.1 Therapeutic indications**

Disease of the cardiovascular system (e.g. an adjunct in the treatment of pulmonary oedema or paroxysmal nocturnal dyspnoea caused by left ventricular heart failure), reversible airways obstruction including status asthmaticus and acute bronchospasm.

##### **4.2 Posology and method of administration**

Aminophylline Injection BP may be given by slow intravenous injection or intravenous infusion in glucose injection or sodium chloride injection. It has also been given by deep intramuscular injection in a dose of 500mg in 2mls of water for injections, but such injections are painful.

Aminophylline has a low therapeutic index, therefore cautious dosage determination is essential. Therapeutic serum concentrations of theophylline are considered to range from 10 to 20 mcg/ml and levels greater than 20 mcg/ml are often associated with toxic effects. A range of 5 to 15 mcg/ml may be effective, and associated with fewer adverse effects.

## **In patients NOT currently receiving theophylline preparations**

To minimise adverse effects, IV Aminophylline should be administered slowly, at a rate not exceeding 25mg Aminophylline per minute, up to a dose of 250-500mg (5mg/kg). If patients experience acute adverse effects while loading doses are being infused, the infusion may be stopped for 5-10 minutes or administered at a slower rate.

### Approximate IV Aminophylline Maintenance Doses

*n.b. The use of Aminophylline IV in children under 6 months of age is not generally recommended.*

<u>Group</u>	<u>Maintenance Dose</u>
Children 6 months to 9 years of age	1mg/kg/hour
Children 10-16 years of age and young adult smokers	0.8mg/kg/hour
Otherwise healthy non-smoking adults	0.5mg/kg/hour
Elderly patients	0.3mg/kg/hour

## **In patients currently receiving theophylline preparations**

In patients who are currently receiving theophylline preparations, the time, route of administration and dosage form of the patient's last dose should be determined where possible and considered in determining a loading dose. Loading doses are based on the expectation that 0.5mg/kg (lean body weight) of theophylline will result in a 1 microgram/ml increase in serum theophylline concentration. Therefore, in patients currently receiving theophylline preparations, the loading dose should be deferred until a serum theophylline concentration can be attained or the clinician must carefully select a dose based on the potential benefits and risks.

Subsequently, the approximate IV aminophylline maintenance doses described above may be considered.

**Elimination of theophylline in children younger than 6 months of age, especially in neonates, appears to be reduced. Because of this variation in metabolism the use of Aminophylline injection in children under 6 months of age is not generally recommended.**

### **4.3 Contra-indications**

Aminophylline injection should not be used in patients hypersensitive to ethylenediamine or those allergic to the theophyllines, caffeine or theobromine.

Aminophylline should not be administered concomitantly with other xanthine drugs. When therapeutic doses of Aminophylline and/or theophylline are administered simultaneously by more than one route or in more than one preparation, the hazard of serious toxicity is increased.

The use of Aminophylline IV in children under 6 months of age is not generally recommended.

The use of Aminophylline is contra-indicated in patients with acute porphyria.

### **4.4 Special warnings and precautions for use**

Intravenous Aminophylline must be administered very slowly to prevent dangerous central nervous system and cardiovascular side-effects due to direct stimulating effect of Aminophylline.

Aminophylline has a low therapeutic index and serum levels should be monitored regularly, particularly during initiation of therapy.

Aminophylline injection should be administered cautiously to young children and to patients over 55 years of age.

Caution is also advised in patients undergoing influenza immunisation or who have active influenza infection or acute febrile illness.

Aminophylline should be given with caution to patients with cardiac failure, chronic obstructive pulmonary disease, renal or hepatic dysfunction and in chronic alcoholism since clearance of Aminophylline is decreased.

Theophylline clearance may be increased in smokers and in those regularly exposed to tobacco smoke.

During regular therapy serum potassium levels must be monitored. This is essential during combination therapy with beta2-agonists, corticosteroids or diuretics, or in the presence of hypoxia.

Aminophylline should be used with caution in patients with peptic ulcer, hyperthyroidism, glaucoma, diabetes mellitus, severe hypoxaemia, hypertension, compromised cardiac or circulatory function and epilepsy, as these conditions may be exacerbated.

## 4.5 Interactions with other medicinal products and other forms of interactions

The following drugs may **increase** plasma theophylline concentrations:

- Cimetidine
- Macrolide antibiotics (e.g. erythromycin, clarithromycin)
- Quinolone antibiotics (e.g. ciprofloxacin, norfloxacin)
- Fluconazole
- Isoniazid
- Propranolol
- Allopurinol (high doses e.g. 600 mg daily)
- Oral contraceptives
- Mexiletine, propafenone
- Calcium channel blockers, diltiazem, verapamil
- Fluvoxamine
- St John's Wort (*Hypericum perforatum*)
- Disulfiram
- Interferon alfa, influenza vaccine
- Methotrexate
- Zafirlukast

The following drugs may **decrease** plasma theophylline concentrations:

- Rifampicin
- Antiepileptics (e.g. carbamazepine, phenytoin, primidone, phenobarbitone)
- Ritonavir
- Aminoglutethimide
- Sulphinpyrazone

Other interactions:

### *Xanthines*

Concurrent use of other xanthine derivatives, including theophylline and pentoxifylline are contraindicated due to the risk of toxicity.

### *Lithium*

Aminophylline increases the excretion of lithium and may decrease its therapeutic effectiveness.

*Benzodiazepines:* Theophylline may reduce the effects of benzodiazepines

### *Quinolones*

Increased risk of convulsions.

### *General anaesthetics*

Increased risk of convulsions with ketamine; increased risk of arrhythmias with halothane

*Pancuronium*

Resistance to neuromuscular block with pancuronium has been reported in patients receiving aminophylline.

*Sympathomimetics*

Aminophylline may exhibit synergistic toxicity with ephedrine and other sympathomimetics and concurrent use may dispose the patient to cardiac arrhythmias.

*Beta<sub>2</sub>-adrenergic agonists*

Increased risk of cardiac arrhythmias (see also hypokalaemia).

*Beta-blockers*

Antagonism of bronchodilator effects.

*Cardiac glycosides*

The direct stimulatory effect of Aminophylline on the myocardium may enhance the sensitivity and toxic potential of the cardiac glycosides.

*Adenosine:* The anti-arrhythmic effect of adenosine is antagonised by theophylline

*Leukotriene antagonists:* In clinical trials co-administration with theophylline resulted in decreased plasma levels of zafirlukast, by approximately 30%, but with no effect on plasma theophylline levels. However, during post-marketing surveillance, there have been rare cases of patients experiencing increased theophylline levels when co-administered zafirlukast (see above).

*Doxapram*

Increased CNS stimulation.

*Hypokalaemia*

The hypokalaemic effects of beta<sub>2</sub>-adrenergic agonists may be potentiated by concomitant treatment with aminophylline. There is an increased risk of hypokalaemia when theophylline derivatives are given with corticosteroids or diuretics (see 4.4 Special warnings and precautions for use).

## **4.6 Pregnancy and lactation**

Animal reproduction studies have not been performed with theophyllines. It is not known whether theophyllines can cause foetal harm when administered to pregnant women. Although the safe use of theophylline during pregnancy has not been established relative to potential risk to the foetus, theophyllines have been used during pregnancy without teratogenicity or other adverse foetal effect.

Because of the risk of uncontrolled asthma, their safety during pregnancy when clearly needed is generally not seriously questioned. Theophylline is distributed into milk and may occasionally induce irritability or other signs of toxicity in nursing infants, and therefore should not be used if the mother is breast-feeding her infant.

#### **4.7 Effects on ability to drive and use machines**

None known.

#### **4.8 Undesirable effects**

Adverse events are usually a consequence of gastrointestinal irritation, stimulation of the central nervous system and effects on the cardiovascular system. Hypotension, arrhythmias and convulsions may follow intravenous injection, particularly if the injection is too rapid, and sudden deaths have been reported. Severe toxicity may occur without preceding milder symptoms (see also 4.9 Overdose).

*Immune system:*

Hypersensitivity reactions (see also Skin and subcutaneous tissue disorders).

*Nervous system/Psychiatric:*

Headache, insomnia, confusion, restlessness, hyperventilation, anxiety, vertigo/dizziness, tremor. Higher doses may lead to maniacal behaviour, delirium and convulsions.

*Eye disorders:*

Visual disturbances.

*Cardiac:*

Palpitations, tachycardia, cardiac arrhythmias, hypotension.

*Gastrointestinal:*

Nausea, vomiting, abdominal pain, diarrhoea, gastro-oesophageal reflux, gastrointestinal bleeding.

*Skin and subcutaneous tissue disorders:*

Rash, maculo-papular rash, erythema, pruritus, urticaria, exfoliative dermatitis.

*General/Administration site reactions:*

Intramuscular injections are painful, the pain lasting several hours.

Higher doses may result in hyperthermia and extreme thirst.

## 4.9 Overdose

Aminophylline 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.

Fatalities in adults have occurred during IV Aminophylline administration in large doses in patients with renal, hepatic or cardiovascular complications or where the injection has been given rapidly.

### Symptoms

Tachycardia, in the absence of hypoxia, fever or administration of sympathomimetic drugs, may be an indication of theophylline toxicity. Anorexia, nausea and occasional vomiting, diarrhoea, insomnia, irritability, restlessness and headache commonly occur. Agitation and hallucinations may occur. Patients may experience extreme thirst, slight fever, dilated pupils, tinnitus, palpitations, arrhythmias, haematemesis, albuminuria, hyperglycaemia, hyperthermia and metabolic acidosis. Supraventricular and ventricular arrhythmias and hypotension may occur. Seizures may occur even without preceding symptoms of toxicity and often result in death. Profound hypokalaemia may develop rapidly.

### Treatment

Treatment of overdosage is supportive and symptomatic. Serum theophylline and potassium levels should be monitored. Repeated oral administration of activated charcoal enhances the elimination of theophylline from the body even after intravenous administration. Aggressive antiemetic therapy may be required to allow administration and retention of activated charcoal.

Seizures may be treated with IV diazepam 0.1-0.3mg/kg up to 10mg. Restoration of fluid and electrolytes balance is necessary. Hypokalaemia should be corrected by intravenous infusion of potassium chloride. Sedation with diazepam may be required in agitated patients.

Propranolol may be administered intravenously to reverse extreme tachycardia, hypokalaemia and hyperglycaemia provided the patient does not suffer from asthma.

In general, theophylline is metabolised rapidly and haemodialysis is not warranted. In patients with congestive heart failure or liver disease, haemodialysis may increase theophylline clearance by as much as 2-fold.

*Charcoal haemoperfusion should be considered if:*

- Ileus/ intestinal obstruction prevents administration of multiple dose activated charcoal.
- Plasma theophylline concentration > 80mg/L (acute) or > 60mg/L (chronic). In infants under 6 months of age or the elderly, charcoal haemoperfusion should be considered at theophylline concentrations >40 mg/L. Clinical features rather than theophylline concentration are the best guide for treatment.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Aminophylline is a soluble derivative of theophylline and is given for its theophylline activity. Aminophylline relaxes smooth muscle and relieves bronchial spasm. It stimulates the myocardium and reduces venous pressure in congestive heart failure, leading to a marked increase in cardiac output. It has stimulant effect on respiration, and also a diuretic action of short duration.

### **5.2 Pharmacokinetic properties**

None stated.

### **5.3 Preclinical safety data**

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

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Ethylenediamine Ph. Eur.  
Water for Injections Ph. Eur.

### **6.2 Incompatibilities**

Aminophylline injection is not stable in solutions having a pH of substantially less than 8, however, the drug appears to be relatively stable in large volume parenteral solutions over a wide pH range (3.5-8.6) if Aminophylline concentrations do not exceed 40mg per ml. The activity of alkali-sensitive drugs will be reduced by Aminophylline, these drugs should not be added to IV fluids containing Aminophylline.

**6.3 Shelf life**

36 months.

**6.4 Special precautions for storage**

None stated.

**6.5 Nature and contents of container**

10ml clear glass ampoules, packed in cardboard cartons to contain 10 ampoules

**6.6 Instructions for use, handling and disposal**

Use as directed by a physician.

**ADMINISTRATIVE DATA**

**7. MARKETING AUTHORISATION HOLDER**

hameln pharmaceuticals ltd  
Gloucester  
UK

**8. MARKETING AUTHORISATION NUMBER**

PL 1502/0009R

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION**

12<sup>th</sup> February 1990/ 11<sup>th</sup> September 2002

**10. DATE OF (PARTIAL) REVISION OF TEXT**

06/07/10