1. **NAME OF THE MEDICINAL PRODUCT**
   
   Aminophylline Injection BP

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
   
   Each ml contains 25mg of Aminophylline Ph Eur
   
   For the full list of excipients, see section 6.1.

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.
   
   Aminophylline has a narrow 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.
   
   The dosage should be titrated for each individual and adjusted with caution. Serum theophylline levels should be monitored to ensure that they remain within the therapeutic range. During therapy, patients should be monitored carefully for signs of toxicity.

   **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 recommended.**

   **Use 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 recommended.*

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

**Use 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.

**4.3 Contraindications**

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 recommended.

The use of Aminophylline is contraindicated 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 narrow therapeutic index and serum levels should be monitored regularly, particularly during initiation of therapy.

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

Children are particularly susceptible to the effects of theophylline and care is required when administrating 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.

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.

Aminophylline should not be administered concurrently with other xanthine medications.

4.5 Interactions with other medicinal products and other forms of interactions

The following drugs may increase plasma theophylline concentrations:
• Fluvoxamine

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.

• 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
• St John’s Wort (Hypericum perforatum)
• Disulfiram
• Interferon alfa, influenza vaccine
• Methotrexate
• Zafirlukast
• Thyroid hormones

The following drugs may decrease plasma theophylline concentrations:

• Rifampicin
• Antiepileptics (e.g. carbamazepine, phenytoin, primidone, phenobarbitone)
• Ritonavir
• Aminoglutethimide
• Sulfinpyrazone

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.

**Beta2-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 beta2-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 Fertility, pregnancy and lactation

**Pregnancy**
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. As with other drugs, aminophylline should only be used during pregnancy if considered essential by the physician. Theophylline crosses the placenta.

**Breast-feeding**
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.

**Fertility**
Animal reproduction studies have not been performed with theophyllines

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

**Metabolism and nutrition disorders:**
Metabolic disturbances such as hypokalaemia, hypophosphataemia, and hyponatraemia may occur.

**Nervous system/Psychiatric disorders:**
Headache, insomnia, confusion, restlessness, hyperventilation, anxiety, vertigo/dizziness, tremor. Higher doses may lead to maniacal behaviour, delirium and convulsions.

**Eye disorders:**
Visual disturbances.

**Cardiac disorders:**
Palpitations, tachycardia, cardiac arrhythmias, hypotension.

**Gastrointestinal disorders:**
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:**
Higher doses may result in hyperthermia and extreme thirst.

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

### 4.7 Overdose

Aminophylline has a narrow 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.

**Gastro-intestinal symptoms:**
Anorexia, nausea, vomiting, diarrhoea, and haematemesis.

**Neurological symptoms:**
Restlessness, insomnia, irritability, headache, agitation, hallucinations, extreme thirst, slight fever, dilated pupils, and tinnitus. Seizures may occur even without preceding symptoms of toxicity and often result in death. Coma may develop in very severe cases.

**Cardiovascular symptoms:**
Palpitations, arrhythmias, hypotension, supraventricular and ventricular arrhythmias may occur.

**Metabolic symptoms:**
Hypokalaemia can develop rapidly and may be severe. Hyperglycaemia, albuminuria, hyperthermia, hypomagnesaemia, hypophosphataemia, hypercalcaemia, respiratory alkalosis and metabolic acidosis may also occur. Rhabdomyolysis may also occur.

**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. Pre-clinical 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 now 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. Special precautions for disposal and other handling

Use as directed by a physician.

7. MARKETING AUTHORISATION HOLDER

Hameln Pharmaceuticals Limited
Gloucester
UK

8. MARKETING AUTHORIZATION NUMBER(S)

PL 01502/0009R

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
10 DATE OF REVISION OF THE TEXT

23/01/2015