Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Aminophylline Hydrate 25mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10ml of solution contains 250mg of Aminophylline Hydrate equivalent to 239.73mg of Aminophylline.
Each 1ml of solution contains 25mg Aminophylline Hydrate equivalent to 23.973 mg of Aminophylline.

For the full list of excipients, see section 6.1

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

Posology
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 Section 4.4, Special warnings and precautions for use).

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 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.

Paediatric population
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. The safety and efficacy of aminophylline in children aged less than one year has not yet been established. No data are available (see Section 4.3 Contraindications).

Maintenance dosage:
The following table gives guidance for maintainence 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

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance, ethylenediamine, xanthines or any of the excipients listed in section 6.1.

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 1 year of age is not recommended.

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

4.4 Special warnings and precautions for use

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 (see Section 4.2).

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

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

Paediatric population
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.

Caution is also advised in patients undergoing influencza 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 Interaction with other medicinal products and other forms of interaction

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. 600mg/day)
- Oral contraceptives
- Mexiletine, propafenone
- Calcium channel blockers, diltiazem, verapamil
- 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.
- St John's Wort (Hypericum perforatum)
- Disulfiram
- Interferon alfa, influenza vaccine
- Methotrexate
- Zafirlukast
- Thiabendazole

The following drugs may decrease plasma theophylline concentrations:

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

- Sulphinpyrazone
- Glucagon: Care should be taken in its concomitant use with glucagon as it will potentiate the effects of aminophylline.
- 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 2-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).

Regadenoson:
Aminophylline may prolong a seizure or cause multiple seizures because of its proconvulsant effect. Therefore administration of aminophylline solely for the purpose of terminating a seizure induced by Regadenoson is not recommended.

4.6 Fertility, pregnancy and lactation

This is product should not be administrated 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 ability to drive and use machines

Aminophylline has no or negligible influence on the ability to drive and use machines.

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 Section 4.9 Overdose).

The following adverse reactions are classified by system organ class and ranked under heading of frequency:
Not known (cannot be estimated from the available data)

System organ class	Frequency	Adverse events
Immune system disorders	Not Known	Hypersensitivity (see also Skin and subcutaneous tissue disorders).
Psychiatric disorders	Not Known	Anxiety, insomnia. Higher doses may lead to maniacal behaviour, and delirium.
Nervous system disorders	Not Known	Headache, confusion, restlessness, hyperventilation, vertigo/dizziness, tremor. Higher doses may lead to seizure.
Eye disorders	Not Known	Visual impairment
Cardiac disorders	Not Known	Palpitations, tachycardia, arrhythmia, hypotension.
Gastrointestinal disorders	Not Known	Nausea, vomiting, abdominal pain, diarrhoea, gastro-oesophageal reflux disease, gastrointestinal haemorrhage.
Skin and subcutaneous tissue disorders	Not Known	Rash, rash maculo-papular, erythema, pruritus, urticaria, dermatitis exfoliative.
General disorders and administration site conditions	Not Known	Intramuscular injections are painful, the pain lasting several hours. Higher doses may result in hyperthermia and 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
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 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.

Doses 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.

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.

Warning: Serious features may develop as long as 12 hours after overdosage with sustained release formulations.

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

Neurological: 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: Palpitations, arrhythmias, hypotension, supraventricular and ventricular arrhythmias may occur.

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

Management:

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. 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 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

Pharmacotherapeutic group: Xanthines, ATC code: R03DA05

Mechanism of Action:

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

Theophylline is a smooth muscle relaxant and it relaxes smooth muscles of bronchial airways.

Other actions of theophylline include myocardial stimulation and reduction in 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

Distribution
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.

Biotransformation and Elimination
Theophylline is metabolized 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 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.

Once opened: the product should be used immediately after opening.

6.4 Special precautions for storage

Dot not store above 25°C.
Keep ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only.

Discard the ampoule if the contents are discoloured.

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

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals (Ireland) Ltd
4045 Kingswood Road
Citywest Business Park
Co Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0073/099/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st September 1988

Date of last renewal: 1st September 2008

10 DATE OF REVISION OF THE TEXT

October 2020