1. NAME OF THE MEDICINAL PRODUCT

Phylline Injection BP 25mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Aminophylline (as Dihydrate) BP 25mg

Eq.toAnhydrous Theophylline 19.7mg

Water for Injection BP q.s.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Liquid Injection

Clear, colourless solution filled in transparent glass ampoules.

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

Posology

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 THEOPHYILINE 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 lmg/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.

Method of administration
Aminophylline Injection BP 25mg/ml 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in below.
Hypersensitivity to the 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

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.

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. Elderly patients or those with cardiac or hepatic disease should be monitored carefully for signs of theophylline toxicity. Paediatric population

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.

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

Care should be taken 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.

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 and compromised cardiac or circulatory function, as these conditions may be exacerbated.

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.

4.5 Interaction with other medicinal products and other forms of interaction

The following drugs may decrease Aminophylline clearance resulting in increased plasma theophylline concentrations and the potential for increased toxicity:

- 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
▪ Tacrine
▪ Thiabendazole
▪ Thyroid hormones

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$_2$-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 beta$_2$-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 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

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 breast 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

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

4.8 Undesirable effects

Aminophylline may cause 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 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).
Metabolism and nutrition disorders	Not Known	Metabolic disturbances such as hypokalaemia, hypophosphataemia, and hyponatraemia may occur.
Psychiatric disorders	Not Known	Anxiety, insomnia. Higher doses may lead to maniacal behaviour, and delirium.
Nervous system disorders	Not Known	Headache, confusional state, 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

Healthcare professionals are requested to report any suspected adverse reactions via national Pharmacovigilance Electronic Reporting Systems to the respective national regulatory authorities.

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 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.

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 0.1-0.3mg/kg up to 10mg. Restoration of fluid and electrolytes balance is necessary. Hypokalemia 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 Class: 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 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, 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 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.

Biotransformation and Elimination

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

Water for Injections BP

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

24 Months

6.4 Special Precautions for Storage

Store at a temperature not exceeding 30°C. Protect from light.

6.5 Nature and Contents of Container

10 x 10ml Ampoule packed in a carton along with pack insert.

6.6 Special precautions for disposal and other 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

Syner-Med Pharmaceuticals (Kenya) Limited
Address: Gayatri House ICD Road, Off Mombasa Road,
Nairobi KENYA
MANUFACTURING SITE ADDRESS
Scott-Edil Pharmacia Ltd.
56, EPIP, Phase-I, Jharmajri, Baddi-173205, (HP), INDIA

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