Prescribing Information (Summary of Product Characteristics)

1. NAME OF MEDICINAL PRODUCT

Phylline

2. Qualitative and Quantitative Composition

Each ml contains:
Aminophylline BP 25 mg
Water for Injections BP q.s.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection

Description: A clear and colourless solution free from visible particles and fibers.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Indication

Disease of the cardiovascular system (e.g., an adjunct in the treatment ofpulmonary 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 maybe 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 25 mg 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 510 minutes or administered at a slower rate.

Approximate IV Aminophylline Maintenance Doses

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

Group	Maintenance Dose
Children 6 months to 9 years of age	1mg/kg/hour
Children 1016 years of age and young adult smokers	0.8mg/kg/hour
Otherwise healthy nonsmoking adults	0.5mg/kg/hour
Elderly patients	0.3mg/kg/hour

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 describedabove 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 directstimulating 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 55years of age.

Children are particularly susceptible to the effects of theophylline and care is required when administrating aminophylline to children. There have beenreports 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 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

FORMS OF INTERACTION

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 (Hypericumperforatum)
• 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 andpentoxifylline are contraindicated due to the risk of toxicity.
Lithium
Aminophylline increases the excretion of lithium and may decrease itstherapeutic effectiveness.
Benzodiazepines: Theophylline may reduce the effects of benzodiazepinesQuinolones
Increased risk of convulsions.General anaesthetics
Increased risk of convulsions with ketamine; increased risk of arrhythmiaswith halothane
Pancuronium
Resistance to neuromuscular block with pancuronium has been reported inpatients 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

4.6 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 ifthe 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

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.

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.

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.

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 doses 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.

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 providers are asked to report any suspected adverse reactions to the marketing authorization holder or if available via the national reporting system (See details below);

Paper based reporting: TMDA yellow card
Online reporting: https://sqrt.tmda.go.tz/
*USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions.*

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMICS 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

Aminophylline dissociates rapidly to theophylline in biological fluids. Theophylline is rapidly distributed throughout non-adipose tissues and extracellular fluids. Theophylline crosses the placenta, and is distributed into breast milk. The concentration of theophylline in breast milk is approximately

70% that found in the serum. The apparent volume of distribution of theophylline is 0.3 to 0.7 L/kg (average 0.45 L/kg). Approximately 60% of theophylline in adults and 35% in premature infants and neonates is bound to plasma proteins.

Theophylline undergoes hepatic metabolism via the cytochrome P450 system. In adults the main metabolites are 1,3-dimethyl uric acid, 1-methyl uric acid, and 3-methylxanthine. Theophylline and its metabolites undergo renalexcretion.

There is significant interpatient variability in the pharmacokinetics of theophylline, and hence aminophylline. The serum half-life of theophylline in otherwise healthy, non-smoking, asthmatic adults' averages 7 to 9 hours, and theophylline clearance in this group is reported to be approximately 0.65mL/kg/hr. Serum half-life is increased and clearance decreased in the elderly and in patients with congestive heart failure, chronic obstructive pulmonary disease, cor pulmonale or liver disease. Serum half-life is decreased and clearance increased in cigarette or marijuana smokers. Clearance in premature infants and neonates is reduced. Theophylline clearance increases during the first year of life and remains relatively constant during the first 9 years, then gradually declines to adult values by 16 years of age.

Theophylline, (and hence aminophylline), has a low therapeutic index. Serum theophylline concentrations of around 5 to 20 microgram/mL (27.5 to 110 micromole/L) are generally considered therapeutic. Serum theophylline concentrations greater than 20 microgram/mL (110 micromoles/L) are often associated with adverse reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS (S)

Ethylenediamine BP
Water for Injections BP

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

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a dry place, below 30°C. Protect from light. **KEEP OUT OF REACH OF CHILDREN.**

6.5 NATURE AND CONTENTS OF CONTAINER

5 x 10 ml plain glass ampoules (USP type-1) are packed in the carton along with Tray and insert.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SWISS PARENTERALS LTD.
808, 809 & 810, Kerala Industrial Estate, GIDC,Nr. Bavla,
City: Ahmedabad
Dist. Ahmedabad-382 220
Gujarat, India.

8. MARKETING AUTHORISATION NUMBER

TAN 20 HM 0415

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

25/09/2020

10. DATE OF REVISION / APPROVAL OF THE TEXT