Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Phyllocontin 225 mg Prolonged Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains aminophylline hydrate 225 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablets.
Pale yellow, round, film-coated tablets plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment and prophylaxis of bronchospasm and inflammation associated with asthma, emphysema and chronic bronchitis. Also indicated in adults for the treatment of cardiac asthma and left ventricular or congestive cardiac failure.

PHYLLOCONTIN tablets are indicated for use in adults and children aged 6 years and above. Aminophylline should not be used as the first drug of choice in the treatment of asthma in children.

4.2 Posology and method of administration

Posology

Adults and the elderly
The usual maintenance dose is one PHYLLOCONTIN tablet 225 mg twice daily. This may be titrated to higher dosage as required.

Paediatric population aged 6 years and above
The usual paediatric maintenance dose is 10 mg/kg twice daily.

Some children with chronic asthma require and tolerate much higher doses (11-18 mg/kg twice daily).

Clearance is increased in children compared to values observed in adult subjects. The rapid clearance observed in children decreases towards adult values in late teens. Therefore lower doses may be required for adolescents.

Aminophylline should not be administered to children less than 6 years of age (approximately 22 kg). Other dosage forms are available that are more suitable for children less than 6 years of age.

Theophylline distributes poorly into body fat, therefore mg/kg doses should be calculated on the basis of lean (ideal) body weight.

Plasma theophylline concentrations should ideally be maintained between 5 and 12 mcg/mL. A plasma level of 5 mcg/mL probably represents the lower level of clinical effectiveness. Significant adverse reactions are usually seen at plasma theophylline levels greater than 20 mcg/mL.

Monitoring of plasma theophylline concentrations may be required when: higher doses are prescribed; patients have co-morbidities resulting in impaired clearance; when aminophylline is co-administered with medication that reduces theophylline clearance.

Method of administration Oral.
The tablets should be swallowed and not chewed.

Missed dose
If a patient forgets to take a dose but remembers within 4 hours of the time the dose was due to be taken, the tablets can be taken straight away. The next dose should be taken at the normal time. Beyond 4 hours, the prescriber may need to consider alternative treatment until the dose is due.

4.3 Contraindications

Hypersensitivity to xanthines, ethylenediamine or any of the excipients listed in section 6.1.
Concomitant use with ephedrine in children less than 6 years of age (or less than 22 kg).
Porphyria.
Aminophylline is contraindicated in children under 6 months of age.

4.4 Special warnings and precautions for use

The patient's response to therapy should be carefully monitored – worsening of asthma symptoms requires medical attention.

Due to potential decreased clearance, dose reduction and monitoring of serum theophylline concentrations may be required in elderly patients and patients with:

- cardiac disease
- hepatic disease
- exacerbations of lung disease
- hypothyroidism (and when starting acute treatment)
- fever
- viral infections

Due to potential increased clearance, dose increase and monitoring of serum theophylline concentrations may be required in patients with hyperthyroidism (and when starting acute hyperthyroidism treatment) and cystic fibrosis.

Aminophylline may:

- act as a gastrointestinal tract irritant and increase gastric secretion, therefore caution should be exercised in patients with peptic ulcers.
- exacerbate cardiac arrhythmias and therefore caution should be exercised in patients with cardiac disorders
- exacerbate frequency and duration of seizures and therefore caution should be exercised in patients with history of seizures and alternative treatment considered.

Caution should be exercised in elderly males with pre-existing partial urinary tract obstruction, such as prostatic enlargement, due to risk of urinary retention.

Particular care is advised in patients suffering from severe asthma who require acute aminophylline administration. It is recommended that serum theophylline concentrations are monitored in such situations.

4.5 Interaction with other medicinal products and other forms of interaction

The following increase clearance of theophylline and it may therefore be necessary to increase dosage of aminophylline to ensure a therapeutic effect: aminoglutethimide, carbamazepine, isoprenaline, phenytoin, rifampicin, sulphinpyrazone, barbiturates, ritonavir and hypericum perforatum (St. John's Wort).

Smoking and alcohol consumption can also increase clearance of theophylline.

The following reduce clearance of theophylline and a reduced dosage of aminophylline may therefore be necessary to avoid side-effects: aciclovir, allopurinol, carbimazole, cimetidine, clarithromycin, diltiazem, disulfiram, erythromycin, fluconazole, interferon, isoniazid, methotrexate, mexiletine, nizatidine, pentoxifylline, propafenone, propranolol, thiabendazole, verapamil and oral contraceptives.

Theophylline has been shown to interact with some quinolone antibiotics including ciprofloxacin and enoxacin, which may result in elevated plasma theophylline levels.

The concomitant use of theophylline and fluvoxamine should usually be avoided. Where this is not possible, patients should have their aminophylline dose reduced and plasma theophylline should be monitored closely.

Factors such as viral infections, liver disease and heart failure also reduce theophylline clearance. There are conflicting reports concerning the potentiation of theophylline by influenza vaccine and physicians should be aware that interaction may occur resulting in increased serum theophylline levels. A reduction of dosage may also be necessary in elderly patients. Thyroid disease or associated treatment may alter theophylline plasma levels.

Concurrent administration of aminophylline may:

- inhibit the effect of adenosine receptor agonists (adenosine, regadenoson, dipyridamol) and may reduce their toxicity when used for cardiac perfusion scanning;
- oppose the sedatory effect of benzodiazepines;
- result in the occurrence of arrhythmias with halothane;
- result in thrombocytopenia with lomustine
- increase urinary lithium clearance.

Therefore these drugs should be used with caution.

Care should be taken in its concomitant use with β-adrenergic agonists, glucagon and other xanthine drugs, as these will potentiate the effects of theophylline. The incidence of toxic effects may be enhanced by the concomitant use of ephedrine.

Hypokalaemia resulting from β2 agonist therapy, steroids, diuretics and hypoxia may be potentiated by xanthines. Particular care is advised in patients suffering from severe asthma who require hospitalisation. It is recommended that serum potassium concentrations are monitored in such situations.

Theophylline may decrease steady state phenytoin levels.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from well controlled studies of the use of theophylline/aminophylline in pregnant women. Theophylline has been reported to give rise to teratogenic effects in mice, rats and rabbits (See section 5.3). The potential risk for humans is unknown.

Theophylline should not be administered during pregnancy unless the benefit is considered to outweigh the risk.

Breast-feeding
Theophylline is secreted in breast milk, and may be associated with irritability in the infant, therefore it should only be given to breast feeding women when the anticipated benefits outweigh the risk to the child.

4.7 Effects on ability to drive and use machines

PHYLLOCONTIN tablets have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The following adverse drug reactions have been reported in the post-marketing setting for aminophylline. Frequencies of "not known" have been assigned as accurate frequencies cannot be estimated from the available clinical trial data.

System Organ Class	Frequency not known (cannot be estimated from the available data)
Immune system disorders	Anaphylactic reaction Anaphylactoid reaction Hypersensitivity
Metabolism and nutrition disorders	Hyperuricaemia
Psychiatric disorders	Agitation Anxiety Insomnia Sleep disorder
Nervous system disorders	Convulsions Dizziness Headache Tremor
Cardiac disorders	Atrial tachycardia Palpitations Sinus tachycardia
Gastrointestinal disorders	Abdominal pain Diarrhoea Gastric irritation Gastro-oesophageal reflux Nausea Vomiting
Skin and subcutaneous tissue disorders	Pruritus Rash
Renal and urinary disorders	Diuresis Urinary retention*

*Please refer to section 4.4 as aminophylline may induce urinary retention in elderly males with pre-existing partial urinary tract obstruction.

Reporting of 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, Earlsfort terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; Email: medsafety@hpra.ie.

4.9 Overdose

Theophylline 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.

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.

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

Alimentary symptoms: Nausea, vomiting (which is often severe), epigastric pain and haematemesis. Consider pancreatitis if abdominal pain persists.

Neurological symptoms: Restlessness, hypertonia, exaggerated limb reflexes, convulsions, seizures. Coma may develop in very severe cases.

Cardiovascular symptoms: Hypotension. Sinus tachycardia is common. Ectopic beats and supraventricular and ventricular tachycardia may follow.

Metabolic symptoms: Hypokalaemia due to shift in potassium from plasma into cells is common, can develop rapidly and may be severe. Hyperglycaemia, hypomagnesaemia and metabolic acidosis may also occur. Rhabdomyolysis may also occur.

Management:
Activated charcoal or gastric lavage should be considered if a significant overdose has been ingested within 1-2 hours. Repeated doses of activated charcoal given by mouth can enhance theophylline elimination. Measure the plasma potassium concentration urgently, repeat frequently and correct hypokalaemia. BEWARE! If large amounts of potassium have been given, serious hyperkalaemia may develop during recovery. If plasma potassium is low, then the plasma magnesium concentration should be measured as soon as possible.

Measure the plasma theophylline concentration regularly when severe poisoning is suspected, until concentrations are falling. Vomiting should be treated with an antiemetic such as metoclopramide or ondansetron.

In the treatment of ventricular arrhythmias, proconvulsant antiarrhythmic agents such as lignocaine (lidocaine) should be avoided because of the risk of causing or exacerbating seizures.

Tachycardia with an adequate cardiac output is best left untreated. Beta-blockers may be given in extreme cases but not if the patient is asthmatic.

Control isolated convulsions with intravenous diazepam. Exclude hypokalaemia as a cause.
Particularly in the setting of theophylline overdose induced convulsions, efficacy of some anticonvulsant drugs such as benzodiazepines, may be reduced through suspected pharmacodynamic interactions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airways disease, xanthines
ATC code: R03D A05

Aminophylline (theophylline) is a bronchodilator. In addition it affects the function of a number of cells involved in the inflammatory processes associated with asthma and chronic obstructive airways disease. Of most importance may be enhanced suppressor T-lymphocyte activity and reduction of eosinophil and neutrophil function. These actions may contribute to anti-inflammatory prophylactic activity in asthma and chronic obstructive airways disease.

Theophylline may contribute to the prevention of the late asthmatic inflammatory response due to immunological stimuli.

5.2 Pharmacokinetic properties

Absorption
Following oral administration of PHYLLOCONTIN tablets, the delivery of theophylline is controlled and at steady state, peak concentrations are typically seen after approximately 5 hours.

An effective plasma concentration is considered to be 5-12 micrograms/ml, although plasma concentrations up to 20 micrograms/ml may be necessary to achieve efficacy in some cases. Do no exceed 20 micrograms/ml.

Distribution and protein binding
Theophylline is distributed through all body compartments; approximately 60% is bound to plasma proteins.

Biotransformation
Theophylline is metabolised in the liver to 1, 3 dimethyluric acid, 1 methyluric acid and 3-methylxanthine.

Elimination
Theophylline and its metabolites are excreted mainly in the urine. Approximately 10% is excreted unchanged.

Factors affecting clearance

The predominant factors which alter theophylline clearance are: age, body weight, diet, smoking habits, other drugs and cardiorespiratory or hepatic disease. Clearance is increased in children compared to values observed in adult subjects. Clearance decreases toward adult values in late teens.

5.3 Preclinical safety data

Genotoxicity and carcinogenicity
In vitro and *in vivo* assays have shown both positive and negative genotoxic results for theophylline. However, oral theophylline administered daily to rats and mice for 2 years did not show carcinogenicity. Therefore, it is unlikely that theophylline poses a carcinogenic risk in man.

Reproductive and developmental toxicity
Theophylline has been shown to have effects upon the male reproductive system in rodents, but at doses considered in excess of the maximum human dose indicating little relevance to clinical use.

Several embryofetal development studies in rats, mice and rabbits have demonstrated developmental effects independent from maternal toxicity at high doses of theophylline. Therefore theophylline should be considered to have the potential for developmental toxicity in man.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxyethylcellulose
Cetostearyl alcohol
Talc
Magnesium stearate
Povidone (K25)

Film coating:

Hypromellose
Titanium dioxide (E171)
Iron oxide (E172)
Macrogol 400

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

1. Polypropylene containers with polyethylene lids containing 50, 56, 250 or 1000 tablets.
2. Aluminium foil backed PVC blister strips in cardboard cartons containing 10, 56 or 60 tablets.

Not all pack sizes may be marketed.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ennogen Healthcare (Europe) Limited
Block B
The Crescent Building
Northwood Business Park
Santry
Dublin 9
D09 C6X8
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23369/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1984

Date of last renewal: 01 April 2004

10 DATE OF REVISION OF THE TEXT

July 2025