Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Phyllocontin Continus 225mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Aminophylline Hydrate 225 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated, prolonged-release tablet

Product imported from the UK:
Pale yellow tablets with the Napp logo marked on one side and SA on the other.

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.

4.2 Posology and method of administration

Route of Administration

Oral.
The tablets should be swallowed whole and not chewed or crushed. Chewing or crushing may lead to a rapid release of aminophylline with the potential for toxicity.

Adults
The usual daily dose is two PHYLLOCONTIN CONTINUS tablets 225 mg twice daily following an initial week of therapy on 1 tablet 12-hourly.

Children: The maintenance dose is 12 mg/kg 12-hourly adjusted to the nearest 225 mg. It is recommended that half the maintenance dose be given for the first week of therapy if the patient has not previously been receiving xanthine preparations.

Some children with chronic asthma require and tolerate much higher doses (13-20 mg/kg twice daily). Lower doses (based on the usual adult dose) may be required by adolescents. Phyllocontin Continus tablets 225 mg are not suitable as a starting dose for children weighing under 40 kg.

Elderly
As the elderly may require lower dosages, the dose should be adjusted following the response to the initial week of therapy on 1 tablet 12-hourly.

Dose Titration
Patients vary in their response to xanthines and it may be necessary to titrate dosage individually. Steady state theophylline levels are generally attained 3-4 days after dose adjustment. If a satisfactory clinical response is not achieved, serum theophylline should be measured 4-6 hours after the last dose. Based on serum theophylline assay results dosage should be titrated using the following as a guide:

Peak Serum Theophylline	Dosage Adjustment
<10 mcg ml^{-1}	Increase total daily dose by half
10-15 mcg ml^{-1}	Increase total daily dose by one quarter if symptoms persist
16-20 mcg ml^{-1}	No adjustment required
21-25 mcg ml^{-1}	Decrease dose by one quarter
26-30 mcg ml^{-1}	Miss next dose and decrease maintenance dose by one half

It is advisable to re-check serum theophylline concentration after dose adjustment, when steady state is attained.

4.3 Contraindications

Use in patients with known hypersensitivity to xanthine group of drugs or any other constituents of the tablets. Should not be given concomitantly with ephedrine in children.

4.4 Special warnings and precautions for use

1. Children may be susceptible to mood change and effects on level of cerebral function particularly if the recommended dosage is exceeded.
2. The slow release characteristics of this product should be kept in mind. If intravenous aminophylline administration is required for management of acute episodes, there is a possibility of toxicity from inadvertently high serum levels.
3. Caution should be exercised in patients with cardiac disease. Severe side effects (cramps, convulsions, supraventricular tachycardia) may appear at very high serum concentrations, in which case medication should be discontinued.
4. Care should be taken in patients suffering from insomnia.
5. Viral infections, liver disease, heart failure, cor pulmonale may reduce clearance of theophylline and the dosage should be reduced if necessary.
6. Alternative treatment is advised for patients with a history of seizure activity.
7. It is not possible to ensure bioequivalence between different prolonged release theophylline products. Therefore, patients once titrated to an effective dose, should not be changed from PHYLLOCONTIN CONTINUS tablet preparations to other slow or prolonged release xanthine preparations without re-titration and clinical assessment.

4.5 Interaction with other medicinal products and other forms of interaction

The following increase clearance and it may therefore be necessary to increase dosage to ensure a therapeutic effect: aminoglutethimide, carbamazepine, isoprenaline, moracizine, phenytoin, rifampicin, sulphinpyrazone, barbiturates and *hypericum perforatum*. Plasma concentrations of theophylline can be reduced by concomitant use of the herbal preparation St. John's Wort (*hypericum perforatum*). Smoking and alcohol consumption can also increase clearance of theophylline.

The following reduce clearance and a reduced dosage may therefore be necessary to avoid side-effects: allopurinol, carbimazole, cimetidine, ciprofloxacin, clarithromycin, diltiazem, disulfiram, erythromycin, fluconazole, interferon, isoniazid, methotrexate, mexiletine, nizatidine, norfloxacin, propafenone, propranolol, oxpentifylline, ofloxacin, thiabendazole, verapamil, viloxazine hydrochloride and oral contraceptives. 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.

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. A reduction of dosage may also be necessary in elderly patients. Thyroid disease or associated treatment may alter theophylline plasma levels. There is also a pharmacological interaction with adenosine, benzodiazepines, halothane, lomustine and lithium and 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.

The hypokalaemia resulting from ß2 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 levels are monitored in such situations.

Theophylline may decrease steady state phenytoin levels.

4.6 Fertility, pregnancy and lactation

There are no adequate data from well controlled studies of the use of theophylline in pregnant women. Theophylline has been reported to give rise to teratogenic effects in mice, rats and rabbits (see Section 5.3; preclinical safety data). The potential risk for humans is unknown. Theophylline should not be administered during pregnancy unless the benefit is considered to outweigh the risk. 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

None known

4.8 Undesirable effects

The most common side effects are nausea, vomiting, gastric irritations, anorexia, headaches, CNS stimulation, tachycardia, palpitations, arrhythmias and convulsions. In most cases they disappear by reduction of the dose. If side effects appear, serum theophylline levels should be monitored and maintained between 10 and 20 µg/ml if tolerated.

4.9 Overdose

Symptoms: Overdose with aminophylline may be manifested by symptoms such as vomitting, abdominal pain, acid/base disturbance, rhabdomyolysis, sinus tachycardia, venticular arrhythmias, nervousness and seizures.

Treatment: Empty stomach contents. Monitor electrocardiogram and maintain fluid balance. Oral activated medical charcoal has been found to reduce high theophylline blood levels. In severe poisoning emply charcoal - column haemoperfusion. Treat symptoms on appearance. The psychician should be aware that tablets in the intestine will continue to release theophylline for a period of hours.

In the event of hypokalaemia, potassium chloride should be given by slow intravenous infusion. Repeated measurements of plasma porassium should be made.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Xanthines
ATC code: R03D A05
Aminophylline 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

Aminophylline is a combination of theophylline and ethylenediamine. It is readily absorbed from the gastrointestinal tract. Theophylline, the active moiety, has a half life between 3 and 9 hours. At least 60% of theophylline may be bound to plasma proteins. Theophylline is excreted in the urine as metabolites. Approximately 10% is excreted unchanged.

5.3 Preclinical safety data

In studies in which mice, rats and rabbits were dosed during the period of organogenesis, theophylline produced teratogenic effects.

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

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25^0C. Store in the original package.

6.5 Nature and contents of container

Aluminium foil backed PVC blister strips in cardboard cartons containing 56 tablets.

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 PARALLEL PRODUCT AUTHORISATION HOLDER

B&S Healthcare
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United Kingdom

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1328/31/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 13th October 2006

Dat of Last Renewal: 13th October 2011

10 DATE OF REVISION OF THE TEXT

March 2013