**PHYLLOCONTIN® CONTINUS® Tablets**

**TRADE NAME OF MEDICINAL PRODUCT**
PHYLLOCONTIN® CONTINUS® tablets 225 mg

**QUALITATIVE AND QUANTITATIVE COMPOSITION**
Tablets containing 225 mg of aminophylline hydrate Ph Eur.

**PHARMACEUTICAL FORM**
Pale yellow, film-coated, modified-release tablet with the Napp logo on one side and SA on the other.

**CLINICAL PARTICULARS**

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

**Posology and Method of Administration**

**Route of Administration**
Oral: A controlled-release tablets are not to be chewed or crushed, because that may lead to a rapid release of aminophylline with the potential for toxicity. The tablets may be halved, if required, during the initial week of therapy or for dose titration.

**Children:** The maintenance dose (expressed as mg aminophylline) is 12 mg/kg twice daily adjusted to the nearest 125 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. Not recommended for children under 3 years of age.

**Adults:**
The usual dose is two PHYLLOCONTIN® CONTINUS® tablets 225 mg twice-daily following an initial week of therapy on one tablet twice-daily.

**The elderly:**
The dose should be adjusted following the response to the initial week of therapy on one tablet twice-daily.

**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 adjustments. 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:

<table>
<thead>
<tr>
<th>Peak serum theophylline level</th>
<th>Dosage adjustment to nearest 125 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 micrograms/ml</td>
<td>Increase total daily dose by half</td>
</tr>
<tr>
<td>10-15 micrograms/ml</td>
<td>Increase total daily dose by one quarter if symptoms persist</td>
</tr>
<tr>
<td>16-20 micrograms/ml</td>
<td>No adjustment required</td>
</tr>
<tr>
<td>21-25 micrograms/ml</td>
<td>Decrease dose by one quarter</td>
</tr>
<tr>
<td>26-30 micrograms/ml</td>
<td>Miss next dose and decrease maintenance dose by one half.</td>
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</tbody>
</table>

**Contraindications**
Should not be given concomitantly with ephedrine in children. Use in patients with known hypersensitivity to the xanthine group of drugs.

**Special Warnings and Special Precautions for Use**
A reduction of dosage may be necessary in the elderly patient. Alternative treatment is advised for patients with a history of seizure activity. Caution should be exercised in patients with cardiac disease.

Severe side effects (cramps, convulsions, supraventricular tachycardia) may appear at very high serum concentrations.

It is not possible to ensure bioequivalence between different controlled release theophylline products. Therefore, patients once titrated to an effective dose, should not be changed from theophylline tablets preparations to other slow or sustained release xanthine preparations without re-titration and clinical assessment.

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

The following decrease clearance of theophylline and a reduced dosage of theophylline 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, olofoxacin, thiabendazole, verapamil, vloxyzine 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; 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.

Hypokalemia 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 concentrations are monitored in such situations. Theophylline may decrease steady state phenytoin levels.

A possible drug interaction should be caution in concomitant use of grapefruit or grapefruit juice.

**Pregnancy and Lactation**

Safety in human pregnancy has not been established but it has been in use for many years without apparent ill consequence.

Theophylline crosses the placental barrier and is secreted in breast milk and should be given to breastfeeding women only when the anticipated benefits outweigh the risk to the child.

Use of theophylline during the third trimester, or during breast feeding, may be associated with irritability in the infant. Use in pregnancy only when there is no safe alternative, or when the disease itself carries risk for the mother or child.

**Effects on Ability to Drive and Use Machines**

No known effects.

**Undesirable Effects**

The risk of adverse drug reactions usually associated with theophylline and xanthine derivatives are nausea, gastric irritation, headache, CNS stimulation, tachycardia, palpitations, arrhythmias and convulsions.

**Overdose**

Overdose with theophylline may be manifested by symptoms such as vomiting, abdominal pain, acid/base disturbance, rhabdomyolysis, sinus tachycardia, ventricular arrhythmias, nervousness, and seizures.

Empty stomach contents. Monitor electrocardiogram and maintain fluid balance. Oral activated charcoal has been found to reduce high theophylline serum concentrations. In severe poisoning, employ charcoal-column haemoperfusion. Treat symptoms on appearance. Controlled release tablets may release medication for hours.

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

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamic Properties**

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 stimulates the myocardium and produces a diminution of venous pressure in congestive heart failure leading to marked increase in cardiac output.

**Pharmacokinetic Properties**

Theophylline is distributed through all body compartments, approximately 60% is bound to plasma proteins. It is metabolised in the liver and excreted mainly in the urine as 1, 3 dimethyluric acid, 1 methyluric acid and 3–methylxanthine; approximately 10% is excreted unchanged by a first order process.

The predominant factors which alter theophylline clearance are: age, body weight, diet, smoking habits, other drugs and cardiorespiratory or hepatic disease.

**Preclinical Safety Data**

There are no pre-clinical data of relevance to the prescriber, which are additional to that already included in other sections of the leaflets.

**PHARMACEUTICAL PARTICULARS**

**List of Excipients**

Hydroxyethylcellulose, povidone[k25], cetostearyl alcohol, purified talc and magnesium stearate.

Film coat: hypromellose[E646], polyethylene glycol 400, opaspray M-1-3058 (containing industrial methylated spirit, hypromellose [E464], titanium dioxide [E171],iron oxide [E172].

**Shelf Life**

Three years.

**Special Precautions for Storage**

Store at or below 25°C, in dry place.

**Packaging**

4 to 1000 tablets per securitainer or blister pack.

**MANUFACTURER**

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**MARKETING AUTHORIZATION HOLDER**

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**DISTRIBUTOR**

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