

PRODUCT MONOGRAPH

PrPhyllocontin[®]

PrPhyllocontin[®]-350

Aminophylline sustained release tablets - 225 mg and 350 mg

(equivalent to 182.25 mg & 283.5 mg anhydrous theophylline, respectively)

BRONCHODILATOR

Purdue Pharma
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Pickering, Ontario
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Control No.: 126507

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NAME OF DRUG

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aminophylline sustained release tablets 225 mg & 350 mg

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THERAPEUTIC CLASSIFICATION

Bronchodilator

ACTIONS

Aminophylline is the ethylenediamine salt of theophylline. The pharmacodynamics of **Phyllocontin[®]** and **Phyllocontin[®]-350** (aminophylline sustained release tablets) are a function of theophylline blood levels.

Phyllocontin and **Phyllocontin-350** tablets are sustained release tablets which produce peak blood levels of theophylline between 3 and 5 hours. Once the steady state level has been reached, the therapeutic blood levels persist for 12 hours.

Theophylline is a xanthine structurally related to theobromine and caffeine. It relaxes bronchial smooth muscle (particularly when the muscles are constricted); produces vasodilation except in cerebral vessels; stimulates the CNS including the respiratory center; stimulates cardiac muscle; produces diuresis and increases gastric acid secretion. In addition to its activity as a

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bronchodilator, theophylline may also stimulate mucociliary clearance, inhibit anaphylactic mediator release, suppress mediator-induced inflammation and improve contractility of the diaphragm.

As with other xanthine derivatives, the precise mechanism of action of theophylline has not been determined. Evidence exists indicating that phosphodiesterase inhibition, prostaglandin inhibition, effects on calcium flux and intracellular calcium distribution, and antagonism of endogenous adenosine may all contribute to its pharmacological effects.

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.

INDICATIONS

The symptomatic treatment of reversible bronchoconstriction associated with bronchial asthma, chronic obstructive pulmonary emphysema, chronic bronchitis and related bronchospastic disorders.

CONTRAINDICATIONS

Phyllocontin[®] and **Phyllocontin[®]-350** (aminophylline sustained release tablets) should not be administered to patients with hypersensitivity to xanthines or ethylenediamine, to patients with coronary artery disease where cardiac stimulation might prove harmful or to patients with peptic ulcer.

WARNINGS

Phyllocontin[®] and **Phyllocontin[®]-350** (aminophylline sustained release tablets) are not appropriate for use in an emergency where rapid relief of bronchospasm is required.

Children are very sensitive to xanthines; the margin of safety above therapeutic doses is small.

Phyllocontin and **Phyllocontin-350** tablets are not presently recommended for children under 12 years of age, as a dosage schedule in this age group has not been established.

PRECAUTIONS

There is a marked variation in blood levels achieved in different patients given the same dose of theophylline. High serum levels may occur in some patients receiving doses considered to be conventional. Overdosage may lead to serious side effects such as tachycardia, arrhythmias, seizures, vascular collapse and even death, and may occur without warning signs such as nausea and vomiting. The variability in blood levels is primarily due to differences in the rate of metabolism. Therefore, it is important to individualize the dosage regimen.

Ideally, all individuals should have serum theophylline levels measured and a theophylline half-life calculated which would enable doses and dosing regimens to be tailored to each patient to

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maintain a therapeutic level, to ensure optimal clinical response and to avoid toxicity. The incidence of toxicity increases at serum theophylline levels greater than 82.5 µmol/L (15 µg/mL) and levels above 110 µmol/L (20 µg/mL) are usually quite toxic in most patients (adults). Concurrent tea, coffee or cocoa administration may interfere with analytical results.

The equivalent content of theophylline anhydrous is the active ingredient which determines clinical response. If there is a change in the theophylline product and if it involves a change in the theophylline anhydrous equivalence the physician should adjust the dosage to avoid overdosage or underdosage.

Patients with Special Diseases and Conditions: Theophylline clearance is decreased, which may result in increased serum levels and resultant toxicity in patients:

- with impaired liver or kidney function;
- over 55 years of age, particularly males and those with chronic lung disease;
- with cardiac failure from any cause;
- with active influenza or other viral disease or after influenza immunization;
- with high carbohydrate, low protein diet;
- taking certain drugs (see Drug Interactions, below);
- thyroid disease or associated treatment may alter theophylline plasma levels.

Laboratory monitoring of serum theophylline levels is especially appropriate in the above individuals in order to maintain the appropriate theophylline dosage.

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Theophylline is known to stimulate gastric acid secretion and may also act as a local G.I. irritant. Therefore, the drug should only be used with caution in patients with a history of peptic ulcer disease.

Theophylline may cause arrhythmia and/or worsen pre-existing arrhythmia. Any significant change in rate and/or rhythm warrants monitoring and further investigation.

Many patients who require theophylline may exhibit tachycardia due to their underlying disease process so that the cause/effect relationship to elevated serum theophylline concentrations may not be appreciated.

Use with caution in patients with severe cardiac disease, severe hypoxemia, hypertension, hyperthyroidism, acute myocardial injury, cor pulmonale, congestive heart failure, liver disease, in the elderly (especially males).

Drug Interactions:

A. Theophylline pharmacokinetics are altered by the concurrent use of various drugs as listed below:

Drug	Effect on Theophylline Clearance and Elimination Half-life
Allopurinol, carbimazole, cimetidine, diltiazem, disulfiram, fluconazole, interferon, isoniazid, quinolone antibacterials (ciprofloxacin, norfloxacin, ofloxacin), macrolide antibiotics (erythromycin, clarithromycin, troleandomycin), methotrexate, mexiletine, nizatidine, oral contraceptives, propafenone, propranolol, pentoxiphylline, selective serotonin re-uptake inhibitors (e.g., fluvoxamine), thiabendazole, verapamil, viloxazine hydrochloride	↑ t _{1/2} , ↓ clearance

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Drug	Effect on Theophylline Clearance and Elimination Half-life
Alkalinizing agents	↑ t _{1/2} , ↓ clearance
Influenza vaccine	↑ t _{1/2} , clearance reported to be decreased or no change
Aminoglutethimide, barbiturates, carbamazepine, hypericum perforatum (St. John's Wort), isoproterenol, moracizine, phenytoin, rifampin, sulphinpyrazone	↓ t _{1/2} , ↑ clearance
Tobacco, alcohol	↓ t _{1/2} , ↑ clearance
Acidifying agents	↓ t _{1/2} , ↑ clearance

B. Concurrent use of theophylline influences the actions of certain drugs:

Drug	Influence of Theophylline
Digitalis glycosides	↑ cardiac effect
Thiazides	↑ diuresis
Nephrotoxic drugs	↑ nephrotoxicity
Lithium	↑ ratio of lithium/creatinine clearance, thus a decrease in serum lithium levels
Sympathomimetic amines	↑ toxicity, ↑ CNS stimulation
Coumarin anticoagulants	↓ anticoagulant activity ↑ prothrombin and fibrinogen blood concentrations ↓ prothrombin time
Allopurinol	↓ antihyperuricemic action
Probenicid and pyrazolon derivatives	↓ uricosuric action

There is also a pharmacological interaction with adenosine, benzodiazepines, halothane and lomustine. Care should also be taken in its concomitant use with glucagon and other xanthine drugs.

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Cardiovascular: palpitation, tachycardia, hypotension, circulatory failure, ventricular arrhythmias, extrasystoles and flushing.

Renal: albuminuria, diuresis and hematuria.

Others: hyperglycemia, tachypnea and inappropriate ADH syndrome.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: Treat symptoms on appearance. Sustained release tablets may release medication for hours. Insomnia, restlessness, mild excitement or irritability and rapid pulse are the early symptoms, which may progress to mild delirium.

Sensory disturbances such as tinnitus or flashes of light are common. Anorexia, nausea and vomiting are frequently early observations of theophylline overdose.

Fever, diuresis, dehydration and extreme thirst may be seen. Severe poisoning results in bloody, syrup-like "coffee ground" vomitus, tremors, tonic extensor spasm interrupted by clonic convulsions, extrasystoles, quickened respiration, stupor and finally coma. Cardiovascular disorders and respiratory collapse leading to shock, cyanosis and death follow gross overdoses.

Treatment:

A. If potential oral overdose is established and seizure has not occurred:

- 1) Induce vomiting.

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- 2) Administer a cathartic (this is particularly important when a sustained release preparation has been taken).
- 3) Administer activated charcoal.

B. If patient is having a seizure:

- 1) Establish an airway.
- 2) Administer oxygen.
- 3) Treat the seizure with intravenous diazepam, 0.1 to 0.3 mg/kg up to 10 mg.
- 4) Monitor vital signs, maintain blood pressure and provide adequate hydration.

C. Post Seizure Coma:

- 1) Maintain airway and oxygenation.
- 2) If a result of oral medication, follow the above recommendations to prevent absorption of the drug. Intubation and lavage will have to be performed instead of inducing emesis and the cathartic and charcoal will need to be introduced via a large bore gastric lavage tube.
- 3) Continue to provide full supportive care and adequate hydration while waiting for the drug to be metabolized. In general, the drug is metabolized sufficiently rapidly so as not to warrant consideration of dialysis. However, if serum levels exceed 275 µmol/L (50 µg/mL) charcoal hemoperfusion may be indicated.

DOSAGE AND ADMINISTRATION

Adults: The recommended initial dose is 225-350 mg every 12 hours (equivalent to 182.25 - 283.5 mg anhydrous theophylline).

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Dosage adjustments should be based on the patient's clinical response and/or serum theophylline levels, with increases of 1/2 tablet per dose at 3 to 4 day intervals. Individual requirements vary considerably, therefore, the physician should be prepared to adjust each patient's dose. Doses greater than 1125 mg per day should not be given unless serum theophylline levels are monitored. Monitoring serum theophylline levels is important, especially during dosage adjustment.

At steady-state, **Phyllocontin[®]** and **Phyllocontin[®]-350** (aminophylline sustained release tablets) produce peak theophylline levels 3-5 hours after dosing. For serum levels to be most useful, it is important the patient not have missed any doses during the previous three days. The optimum serum theophylline concentration is in the 44 to 110 $\mu\text{mol/L}$ (8.0 to 20.0 $\mu\text{g/mL}$) range, depending on the severity of the condition. The incidence of adverse effects increases at levels greater than 82.5 $\mu\text{mol/L}$ (15 $\mu\text{g/mL}$). In cases where it is not possible to monitor theophylline levels, patients should be closely observed for signs of toxicity.

Phyllocontin and **Phyllocontin-350** tablets should not be chewed, dissolved or crushed as this may lead to a rapid release of theophylline with the potential for toxicity. Tablets may be halved.

AVAILABILITY

Phyllocontin[®] (sustained release aminophylline tablets) are available in two strengths.

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Phyllocontin[®] - Round, flat-faced, off-white, scored tablets engraved P on one side and PF on the reverse. Contain 225 mg aminophylline U.S.P. (equivalent to 182.25 mg anhydrous theophylline). Supplied in bottles of 100 tablets.

Phyllocontin[®]-350 mg - Square, off-white, scored tablets engraved PF on one side and P 350 on the reverse. Contain 350 mg aminophylline U.S.P. (equivalent to 283.5 mg anhydrous theophylline). Supplied in bottles of 100 tablets.

Store tablets at room temperature (below 30°C).

NON-MEDICINAL INGREDIENTS (*all strengths*): Cetostearyl Alcohol, Hydroxyethyl Cellulose, Magnesium Stearate, Povidone, Talc.

INFORMATION FOR THE PATIENT

Your doctor has prescribed **Phyllocontin[®]/Phyllocontin[®]-350** (aminophylline sustained release tablets), which contain the drug aminophylline incorporated into a sustained release system. Aminophylline opens the airways in your lungs so that you may breathe more easily, and **Phyllocontin's/Phyllocontin-350's** sustained release mechanism gradually releases aminophylline so that most patients need to take **Phyllocontin/Phyllocontin-350** only twice daily.

When Phyllocontin/Phyllocontin-350 should not be used

Phyllocontin/Phyllocontin-350 should not be used if:

- you are allergic to aminophylline, xanthines or ethylenediamine;
- you have coronary heart disease;
- you suffer from peptic ulcers.

Phyllocontin/Phyllocontin-350 tablets, sustained release formulation, are not appropriate for use in an emergency where rapid relief of bronchospasm is required.

Phyllocontin/Phyllocontin-350 is not recommended for use in children under 12 years of age.

You should also inform your doctor if you:

- start or stop smoking;
- are breast-feeding, pregnant or want to become pregnant;
- have impaired liver or kidney function;

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- are over 55 years of age, particularly male and with chronic lung disease;
- have heart disease;
- have influenza or other viral diseases or after influenza immunization;
- have a high carbohydrate, low protein diet;
- are taking certain drugs (see Drug Interactions, below);
- have thyroid disease;
- suffered from seizures (fits or convulsions).

In these situations, your dosage may need to be adjusted.

Drug Interactions

Many medications interact with theophylline, therefore it is important that your doctor knows all the medications which you are taking and if you stop taking them. These include:

- aminoglutethimide, antibiotics, ephedrine, fluconazole, glucagon, halothane, interferons, lithium, lomustine, methotrexate, oral contraceptives or other xanthine drugs;
- if you have had or you are going to have flu injections;
- medicines for alcoholism, asthma, epilepsy, gout, heart problems, insomnia (sleeping problems), stomach ulcers, thyroid problems, tuberculosis;
- St. John's Wort (*Hypericum perforatum*);
- thiabendazole (a drug used for killing worms, for example threadworm and roundworm);
- viloxazine or selective serotonin re-uptake inhibitors, e.g., fluvoxamine (drugs used to treat depression)

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How to take Phyllocontin/Phyllocontin-350

It is important that you take your Phyllocontin/Phyllocontin-350 regularly, at the time and in the exact quantity that your doctor has directed. Do not increase your Phyllocontin/Phyllocontin-350 dose unless specifically directed to do so by your doctor.

To swallow **Phyllocontin/Phyllocontin-350** more easily, and to ensure that the tablets promptly reach your stomach, each dose should be taken with a full glass (120 to 180 mL; 4 to 6 fl. oz.) of water while you are standing or sitting upright. Your tablets should be taken whole or halved (if a dosage containing halved tablets was directed by your doctor), but **do not crush, dissolve or chew** the tablets as this will affect the sustained release mechanism. Unless directed otherwise by your doctor, Phyllocontin/Phyllocontin-350 should be taken with, or shortly following, the evening meal.

Missed doses can cause your symptoms of asthma or bronchitis to reappear and taking more **Phyllocontin/Phyllocontin-350** than prescribed can lead to side effects such as headache, nausea or vomiting. If these side effects occur at any time during **Phyllocontin/Phyllocontin-350** therapy, you should contact your doctor before taking any additional doses. If your symptoms become more severe and you have been taking your medication regularly, you should also contact your doctor.

If you find that you have missed a dose, and less than 4 hours have elapsed since your scheduled dosing time, take your regular dose immediately, then resume taking your regular dose at your next scheduled dosing time. If more than 4 hours have elapsed, call your doctor for advice.

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They may give you another medicine until you are due to take your next tablet.

During a fever or viral infection (e.g., flu), your dosage of **Phyllocontin/Phyllocontin-350** may need to be adjusted. If you develop side effects during such an infection, do not take your next dose of **Phyllocontin/Phyllocontin-350** and call your doctor.

Side effects you may have while taking Phyllocontin/Phyllocontin-350

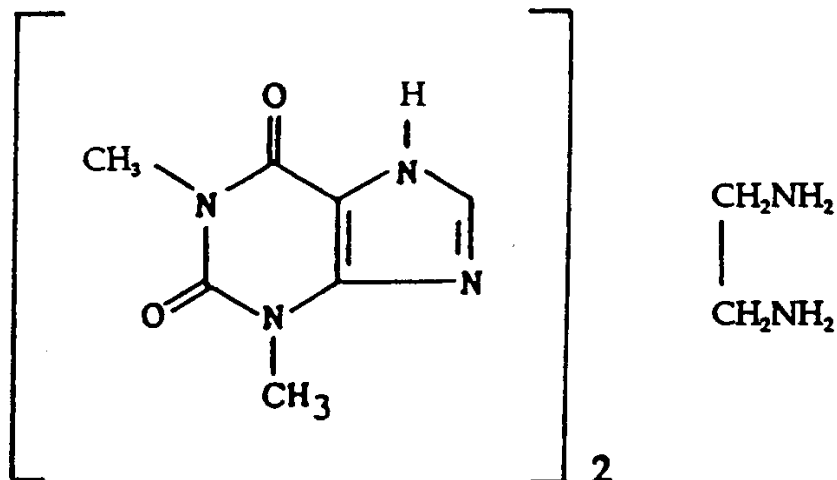
When taking **Phyllocontin/Phyllocontin-350**, you may feel sick, have an upset stomach, loss of appetite, headache, tachycardia or palpitations (a fast, strong heart beat) or arrhythmia (an irregular heart beat). You may also have problems sleeping or feel restless, irritable and shaky. Occasionally, convulsions (fits) have been reported. If any of these problems bother you or you have any other problems, please contact your doctor immediately.

Overdose

In case of a suspected overdose call your doctor or your Regional Poison Control Centre immediately.

CHEMISTRY

Structure:



Aminophylline is a theophylline compound with ethylenediamine (2:1). Aminophylline is anhydrous or contains not more than two molecules of water of hydration.

Molecular Weight: 420.43 (anhydrous)
456.46 (dihydrate)

Description: White or slightly yellow granules with a slight ammoniacal odour and a bitter taste. Soluble in water, insoluble in alcohol and ether.

PHARMACOLOGY

The principal pharmacologic actions of theophylline are to stimulate the central nervous system, act on the kidney to produce diuresis, stimulate cardiac muscle and relax smooth muscle, notably the bronchial muscle.

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Theophylline is usually readily absorbed following oral administration. The extent of absorption is negligibly influenced by food. Following absorption 55-65% of theophylline is reversibly bound to plasma protein. Theophylline is distributed in the extracellular fluids and uniformly to all tissues. The drug has a mean biological half-life of 5.0 hours in adults and 3.5 hours in children with great individual variability. Theophylline is metabolized in the liver. The major metabolites are 1,3-dimethyluric acid, 1-methyluric acid and 3-methylxanthine with only 7 to 13% excreted unchanged.

The enzymes involved in theophylline metabolism are unknown, but do not include xanthine oxidase. Serum uric acid concentrations are not increased during theophylline administration and the drug is not contraindicated in the presence of gout or allopurinol administration. Theophylline clearance is markedly increased in smokers, likely due to stimulation of the metabolizing enzymes.

TOXICOLOGY

The human oral lethal dose is estimated to be from 50 to 500 mg/kg.

Children are more susceptible to the toxic effects of theophylline than adults. The therapeutic serum theophylline concentration for adults is in the range of 44-110 $\mu\text{mol/L}$ (8-20 $\mu\text{g/mL}$). The incidence of adverse effects increases at serum concentrations over 82.5 $\mu\text{mol/L}$ (15 $\mu\text{g/mL}$). Tolerance to some of the toxic effects of theophylline is known to occur.

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BIOAVAILABILITY

In a crossover bioavailability study, 11 male volunteers received single doses of two 225 mg Phyllocontin (aminophylline sustained release) tablets or two 200 mg tablets of a reference sustained release theophylline product (Theo-Dur, Astra). The following mean pharmacokinetic parameters were determined (adjusted to a common dose of 400 mg anhydrous theophylline):

	C_{max} µg/mL	t_{max} hr	AUC_{0-∞} µg.hr/mL	t_½ hr
Phyllocontin 2 x 225 mg	7.9	5.3	161.9	9.7
Reference 2 x 200 mg	7.9	8.6	171.2	9.2

In a separate, multiple dose crossover bioavailability study, 12 volunteers received one 350 mg Phyllocontin-350 tablet q12h or one 300 mg tablet of a reference sustained release theophylline product (Theo-Dur, Astra) q12h for 5 days. Multiple blood samples were obtained following the first dose (Day 1) and following the morning dose after steady- state had been achieved (Day 4). The following mean pharmacokinetic parameters were determined (adjusted to a common dose of 300 mg anhydrous theophylline):

	Day 1		Day 4			
	C_{max} µg/mL	t_{max} hr	C_{max} µg/mL	C_{min} µg/mL	t_{max} hr	AUC_{0-∞} µg.hr/mL
Phyllocontin-350	7.2	5.3	14.9	9.6	4.1	141.1
Reference 300 mg	6.3	7.2	13.4	9.5	5.2	131.0

These studies indicate that Phyllocontin is a reliable sustained release formulation and that, except for a slight difference in t_{max}, Phyllocontin and the reference compound are bioequivalent.

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Clinical Findings:

Following a 48 hour theophylline washout, 25 adult asthmatics began dosing with one 350 mg Phyllocontin-350 tablet q12h. Three days later, morning trough theophylline levels were measured. Fifteen of the patients had trough levels greater than 7.0 µg/mL (38.5 µmol/L) and they continued dosing at one 350 mg tablet q12h. Nine patients had trough theophylline levels below 7.0 µg/mL and their dosage was increased to 1½ 350 mg tablets q12h. Eight of these nine patients has subsequent trough levels greater than 7.0 µg/mL and they continued dosing at 1½ 350 mg tablets q12h. After a further 7 days dosing, all patients returned to multiple serum theophylline measurements following a morning dose. Results by dosage group were:

MEAN STEADY-STATE THEOPHYLLINE LEVELS

Dosage Group	Hours Post-Dose							
	0	1	2	4	5	6	7	8
1 x 350 mg, q12h	8.8	8.8	10.5	11.4	11.3	11.2	10.6	9.5
1½ x 350 mg, q12h	9.9	11.6	13.5	14.3	13.0	11.7	11.7	10.5

This, and other studies demonstrate that individualized dosages of Phyllocontin tablets can maintain therapeutic theophylline concentrations throughout a 12 hour dosage interval. The most frequently reported side effects (>10% incidence), in order of decreasing severity, were: headache, insomnia, nausea, jitteriness and palpitations. All but 2 patients tolerated the side effects and continued the medication following termination of the trial.

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