PRODUCT MONOGRAPH

Pr THEO ER

Theophylline sustained release tablets

House Standard

400 mg and 600 mg

BRONCHODILATOR

AA Pharma Inc.   Date of Preparation:
1165 Creditstone Road, Unit #1   November 30, 2010
Vaughan, Ontario
L4K 4N7

Control Number: 143261

PRODUCT MONOGRAPH

NAME OF DRUG

Pr THEO ER

(Sustained release theophylline tablets 400 mg and 600 mg)

THERAPEUTIC CLASSIFICATION

Bronchodilator

ACTIONS

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

Theo ER (theophylline sustained release tablets) are a sustained release formulation of theophylline. The release system consists of a homogeneous matrix of aliphatic alcohol, cellulose, and active drug. The proportion of these components in the formulation has been chosen to provide gradual, measured release of theophylline by diffusion through the tablet matrix and dissolution. The rate of release of active drug is dependent upon the drug's partition coefficients between the components of the tablet matrix and the aqueous phase within the gastrointestinal tract. The controlled release of theophylline from Theo ER has been demonstrated by both dissolution and phamacokinetic studies.

Theophyllines' mechanism of action is not fully known and 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.

Theophylline is usually well absorbed from the G.I. tract, although there are some differences in the pharmacokinetic behaviour of various sustained release formulations. Theophylline distributes to all body compartments and is approximately 50% protein bound. Elimination is primarily by hepatic biotransformation with approximately 50% excreted as 1,3-dimethyluric acid. Unchanged theophylline, 3-methylxanthine and 1-methyluric acid each account for 10%-15% and 1-methylxanthine is excreted in smaller amounts.

The generally accepted optimal therapeutic serum theophylline concentrations are 10 to 20 mg/L (55 to 110 µmol / L) . Levels above 20 mg/L (110 µmol /L) are usually associated with toxic reactions. The pharmacokinetics of theophylline are influenced by a number of variables such as age, concomitant medications, disease state and smoking (See Precautions). Therefore, each patient's optimal therapeutic maintenance dosage should be determined by individual titration.

At steady-state, theophylline tablets taken once-daily produce peak theophylline levels between 8 and 12 hours post-dose, and trough levels almost always occur at the time of dosing. During once-daily dosing, the mean fluctuation between peak and trough theophylline levels is 130%.

$$\% \text{ Fluctuation} = \left[\frac{C_{max} - C_{min}}{C_{min}} \right] \times 100$$

INDICATIONS

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

CONTRAINDICATIONS

Theo ER (theophylline sustained release tablets) should not be administered to patients with hypersensitivity to xanthines, to patients with coronary artery disease where cardiac stimulation might prove harmful, or to patients with active peptic ulcer.

WARNINGS

In clinical situations where immediate bronchodilation is required, such as status asthmaticus, Theo ER (theophylline sustained release tablets) are not appropriate.

Theophylline has a narrow therapeutic index, the margin of safety above therapeutic doses is small.

Whenever signs of intolerance to theophylline develop, the therapy should be reassessed.

Theophylline clearance can be affected by various disease states, the age of the patient, concomitant use of other medication and lifestyle habits (See Precautions).

A dosage schedule in the pediatric population has not been established. Use of Theo ER in children under 12 years of age is not recommended.

PRECAUTIONS

General: There is a marked variation in serum levels achieved in different patients given the same dose of theophylline. Therefore, high serum levels may occur in some patients receiving doses considered to be conventional. The possibility of theophylline overdose should always be considered. Overdoses of theophylline may cause serious side effects such as tachycardia, arrhythmias, seizures, vascular collapse and even death. These may occur without warning and may not be preceded by less severe side effects such as nausea or restlessness.

The variability in serum levels is primarily due to differences in the rate of metabolism. Therefore, it is advisable to individualize the dosage regimen. Ideally, all patients should have serum theophylline levels measured which would enable doses and dosing regimens to be tailored for each patient in order to maintain therapeutic levels, ensure optimal clinical response and avoid toxicity. The incidence of adverse reactions increases at theophylline levels greater than 15 mg/L (82.5 µmol/L) and levels above 20 mg/L (110 µmol/L) are usually quite toxic in most adults.

Although Theo ER (theophylline sustained release tablets) have pharmacokinetic properties similar to other sustained release theophylline formulations, it is not possible to ensure interchangeability between different formulations. Careful clinical monitoring is required when changing from one formulation to another. The equivalent content of anhydrous theophylline is the active ingredient that determines the blood concentration and clinical response. If a change in theophylline product is made and it involves a change in anhydrous theophylline equivalence, the dose should be adjusted accordingly.

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 of 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 a high carbohydrate, low protein diet;
- patients taking certain drugs such as cimetidine, ciprofloxacin, norfloxacin, erythromycin, troleandomycin and fluvoxamine;
- 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.

Patients who are rapid metabolizers of theophylline, such as the young, smokers and some non-smoking adults may not be suitable candidates for once-daily dosing. In rapid metabolizers, peak to trough fluctuations in theophylline levels may be greater than desirable or result in side-effects at the time of maximum levels and/or the recurrence of symptoms toward the end of the 24 hour dose interval when levels are lowest. In such patients, dividing the total daily theophylline dose into two equal doses may be indicated.

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 ½, ↓ clearance
Alkalinizing agents	↑ t ½, ↓ clearance
Influenza vaccine	↑ t ½, clearance reported to be decreased or no change
Aminoglutethimide, barbiturates, carbamazepine, hypericum perforatum (St. John's Wort), isoproterenol, moracizine, phenytoin, rifampin, sulphinpyrazone	↓ t ½, ↑ clearance
Tobacco, alcohol	↓ t ½, ↑ clearance
Acidifying agents	↓ t ½, ↑ 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
Probenecid and pyrazolone 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.

Hypokalemia resulting from β_2 agonist therapy, steroids, diuretics and hypoxia may be potentiated by xanthines. Particular care is advised in patients suffering from severe asthma who require hospitalization. It is recommended that serum concentrations are monitored in such situations. Theophylline may decrease steady-state phenytoin levels.

Use in Pregnancy and Lactation: Theophylline crosses the placental barrier and also passes freely into breast milk, where concentrations are similar to plasma levels. Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, use of theophylline in pregnant women and nursing mothers should be balanced against the risk of uncontrolled asthma.

Laboratory Test Interactions: When plasma levels are measured by spectrophotometric methods, coffee, tea, cola beverages, chocolate and acetaminophen contribute to falsely high values.

When a high pressure liquid chromatography (HPLC) method is used, plasma theophylline concentrations may be falsely increased by caffeine, some cephalosporins and sulfa medications.

Theophylline may cause elevation of urine catecholamines, plasma uric acid and free fatty acids.

Food Interaction: When immediate release theophylline formulations are administered with food, the rate of absorption is reduced but absorption remains complete. Various sustained release formulations, because of differences in their release mechanisms, may be affected in different ways by concomitant food intake.

Studies have shown that theophylline tablets are more completely absorbed when taken with food as opposed to under fasting conditions (See Bioavailability and Clinical Data).

ADVERSE REACTIONS

The most common adverse reactions are gastric irritation, nausea, vomiting, epigastric pain, and tremor. These are usually early signs of toxicity, however, with high doses ventricular arrhythmias or seizures may be the first signs to appear.

Adverse reactions include:

Gastrointestinal: Nausea, vomiting, epigastric pain, hematemesis, diarrhea, anorexia, intestinal bleeding and reactivation of peptic ulcer.

Central Nervous System: Headache, irritability, restlessness, insomnia, twitching, convulsions and reflex hyperexcitability.

Cardiovascular: Palpitations, 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 also frequently early observations of theophylline overdosage.

Fever, diuresis, dehydration and extreme thirst, acid/base disturbances, rhabdomyolysis, sinus tachycardia and ventricular arrhythmias may be seen. Severe overdosage 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 overdosages.

Treatment:
        A. Monitoring Serum Theophylline Levels
It is important to note that, following the intake of Theo ER (theophylline sustained release tablets), the peak theophylline levels may not occur until eight to twelve hours post ingestion. Moreover, patients ingesting overdoses of sustained release theophylline formulations may also have, after the initial rise in the blood theophylline, a secondary increase in theophylline levels (one report on lethal self-poisoning has attributed this to compacted tablets in the gastrointestinal tract). Following initial treatment, longer careful clinical and laboratory monitoring, including electrocardiograms is advisable after the patient's stabilization.

        B. If a potential oral overdose is established and a seizure has not occurred:
1) Induce emesis.
2) Administer a cathartic (this is particularly important when a sustained release preparation has been taken).
3) Administer activated charcoal.

        C. 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.

D. 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, but 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 50 mg/L (275 µmol/L), charcoal hemoperfusion may be indicated.

DOSAGE AND ADMINISTRATION

Administration and dosing of theophylline should be individualized in respect of the patient's clinical response and serum theophylline levels. There is considerable patient-to-patient variation in the daily theophylline dose required to achieve therapeutic and safe levels. Ideally, all patients should have serum theophylline levels measured which would enable doses and dosing regimens to be tailored in order to maintain therapeutic levels, ensure optimal clinical response and avoid toxicity. Therapeutic serum levels are generally considered to be between 10 and 20 mg/L (55 to 110 µmol/L). Dosage calculations should be based on lean body mass (ideal body weight). A serum level of 20 mg/L (110 µmol/L) is an important reference point in terms of toxicity (See Precautions).

Initial Adult Dose: For patients not currently receiving oral theophylline, the recommended initial dose is 400-600 mg once daily.

In patients currently controlled on oral theophylline, Theo ER (theophylline sustained release tablets) therapy should start at the same daily theophylline dosage (mg for mg basis), provided

by the previous formulation. For example, a patient receiving 400 mg twice daily (800 mg daily dosage), would be given two 400 mg Theo ER once daily. A minimum of 12 hours should elapse between a patient's last dose of the previous oral theophylline formulation and the first dose of Theo ER.

It is recommended that once-daily Theo ER be taken in the evening. Studies have demonstrated that while the bioavailability and the pharmacokinetics of theophylline tablets were not significantly different between morning and evening dosing, a better clinical response was obtained with evening dosing. Subsequent studies indicate that the clinical advantages of evening dosing are likely a result of the maximum theophylline levels occurring in the early morning hours, a time of greatest bronchoconstriction and symptoms for many asthmatics.

It is advisable that Theo ER be taken with food, or within 1-2 hours of mealtime, as studies have suggested that absorption may be incomplete if taken under conditions of prolonged fasting.

Overall, therefore, it is recommended that most patients should take once-daily Theo ER with, or shortly following, the evening meal.

Dose Titration: Dosage adjustments should be based on the patient's clinical response and/or serum theophylline levels, with increases of ½ tablet per day at 3 to 4 day intervals. Individual requirements vary considerably, therefore, the physician should be prepared to adjust each patient's dose. Do not attempt to maintain any dosage that is poorly tolerated.

Monitoring serum theophylline levels is important, especially during initiation of therapy and dosage adjustment. For serum levels to be most useful, it is important that the patient not have missed or added any doses during the previous 3 days and that the dose intervals remained relatively constant. At steady-state, Theo ER produce peak theophylline levels between 8 and 12 hours post-dose, and trough levels almost always occur at the time of dosing. During once-daily dosing, the mean fluctuation between peak and trough theophylline levels is 130%. (See Bioavailability and Clinical Data for further information on the time of peak theophylline levels, and the relationship between a single level obtained 12 hours post-dose and the actual peak level.)

The generally accepted optimal therapeutic range is 10-20 mg/L (55-110 µmol/L), although some patients obtain a very good bronchodilator effect from serum levels less than 10 mg/L (55 µmol/L). In cases where it is not possible to monitor theophylline levels, patients should be closely observed for signs of toxicity and dosages greater than 13 mg/kg/day (or 900 mg/day, whichever is less) should not be given.

Theo ER 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

THEO ER formulated as sustained–release tablets contains anhydrous theophylline with no colour additives. THEO ER is available in 400 mg and 600 mg strengths in bottles of 100.

THEO ER 400 mg: White to off-white, round, flat-faced, bevelled-edge tablets. Engraved "THE" over score "400" on one side.

THEO ER 600 mg: White to off-white, capsule shaped, flat-faced, bevelled-edge tablets. Engraved "THE" over score "600" on one side.

Store tablets at controlled room temperature 15-30°C (59-86°F).

NON - MEDICINAL INGREDIENTS (all strengths): Hydroxypropyl methylcellulose, magnesium stearate and colloidal silicon dioxide.

INFORMATION FOR THE PATIENT
ᴾʳTHEO ER
Theophylline sustained release tablets

Your doctor has prescribed Theo ER (theophylline sustained release tablets), which contain the drug theophylline incorporated into a sustained release system. Theophylline opens the airways in your lungs so that you may breathe more easily, and Theo ER's sustained release mechanism gradually releases theophylline so that most patients need to take Theo ER only once per day.

When Theo ER should not be used

Theo ER should not be used if:
- you are allergic to theophylline or xanthines;
- you have coronary heart disease;
- you suffer from peptic ulcers.

Theo ER tablets, sustained release formulation, are not appropriate for use in an emergency where rapid relief of bronchospasm is required.

Theo ER 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;
- 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).

How to take Theo ER

It is important that you take your Theo ER regularly, at the time and in the exact quantity that your doctor has directed. Do <u>not</u> increase your Theo ER dose unless specifically directed to do so by your doctor.

To swallow Theo ER 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, Theo ER 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 Theo ER than prescribed can lead to side effects such as headache, nausea or vomiting. If these side effects occur at any time during Theo ER 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 6 hours have elapsed since your scheduled dosing time, take your regular dose immediately. If between 6 and 18 hours have elapsed, take ½ your regular dose immediately then resume taking your full regular dose at your next scheduled dosing time. If more than 18 hours have elapsed since your missed dose, wait for your next scheduled dosing time and then resume your regular dosage regimen.

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

Side effects you may have while taking Theo ER

When taking Theo ER, 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:
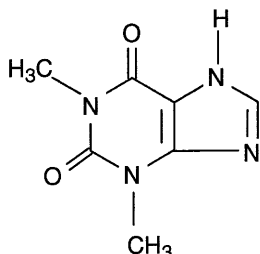
Chemical Name: 1,3 Dimethylxanthine

Molecular Weight: 180.2 (anhydrous)
                     198.2 (monohydrate)

Description: Theophylline is a white, odorless, crystalline powder with a bitter taste. Theophylline is soluble 1:120 in water, 1:80 in alcohol and about 1:200 in chloroform.

PHARMACOLOGY

Pharmacodynamics: 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. The main therapeutic use of theophylline is in the treatment of reversible airway obstruction.

Pharmacokinetics: Theophylline is usually readily absorbed following oral administration. The drug is 55-65% bound to plasma proteins at the therapeutic plasma concentration range of 10 to 20 mg/L (55 to 110 µmol/L); it is not likely to be subject to pronounced displacement effect. In the case of sustained-release products, steady-state plasma concentrations are achieved within 3 days in most patients.

Theophylline is distributed into all body compartments and crosses the placental barrier producing high fetal concentrations. It is also excreted in human breast milk.

Volume of distribution (Vd) ranges from 0.3 to 0.7 L per kg (30-70% ideal body weight) and averages 0.45 L per kg among both children and adults. However, the mean Vd for premature neonates, adults with hepatic cirrhosis or uncorrected acidemia, and the elderly is slightly larger since protein binding is reduced in these patients.

Theophylline is metabolized by the liver to 3-methylxanthine, 1-methyluric acid and 1,3-dimethyluric acid. About 10% of a dose is excreted unchanged in the urine.

The enzymes responsible for theophylline metabolism are unknown but do not include xanthine oxidase. Serum uric acid concentrations do not increase; therefore, the drug is not contraindicated in the presence of either gout or allopurinol administration.

The half-life of theophylline is influenced by a number of known variables. It is prolonged in patients suffering from chronic alcoholism, impaired hepatic or renal function, congestive heart failure, and in patients receiving macrolide antibiotics and cimetidine. Older adults (over age 55) and patients with chronic obstructive pulmonary disease, with or without cor pulmonale, may also have much slower clearance rates. For such patients, the theophylline half-life may exceed 24 hours.

Newborns and neonates have extremely slow clearance rates compared to older infants (over 6 months) and children, and may also have a theophylline half-life of over 24 hours. High fever for prolonged periods may also reduce the rate of theophylline elimination.

Administration of influenza vaccine and infection with influenza virus have been associated with the impaired rate of theophylline elimination and consequent increases in serum theophylline levels, sometimes with toxic symptoms.

The half-life of theophylline in smokers (one to two packs/day) averages four to five hours, much shorter than the half-life in non-smokers which averages seven to nine hours. The increase in theophylline clearance caused by smoking is probably the result of induction of drug-metabolizing enzymes that do not readily normalize after cessation of smoking. It appears that

between three months and two years may be necessary for normalization of the effect of smoking on theophylline pharmacokinetics.

<div align="center">**BIOAVAILABILITY AND CLINICAL DATA**</div>

Bioavailability and Clinical Comparison to Twice-Daily Theophylline:

In a randomized, two-phase crossover trial, 12 asthmatic patients received two weeks therapy with once-daily theophylline (dosed at 2000h) and a twice-daily reference theophylline (dosed at 0800h and 2000h). Asthma symptoms were recorded twice each day. At the end of each two-week treatment, serum theophylline levels were measured every 2 hours over a 24 hour period and spirometry was performed at 2000h, 0600h, and 0800h.

The pharmacokinetic parameters (mean ± SD) and serum theophylline vs. time profiles are shown below:

	Daily Dose mg	Cmax mg/L	Cmin mg/L	Tmax hours	AUC mg.L/hr
Once daily theophylline	783 ±57	15.9 ±4.5	6.5 ±3.1	11.3 ±3.3	271 ±98
Twice daily theophylline	766 ±115	13.4 ±4.8	8.7 ±4.4	6.8 ±3.8	263 ±105

Serum theophylline levels from once-daily theophylline and twice-daily theophylline (mean ± SE):
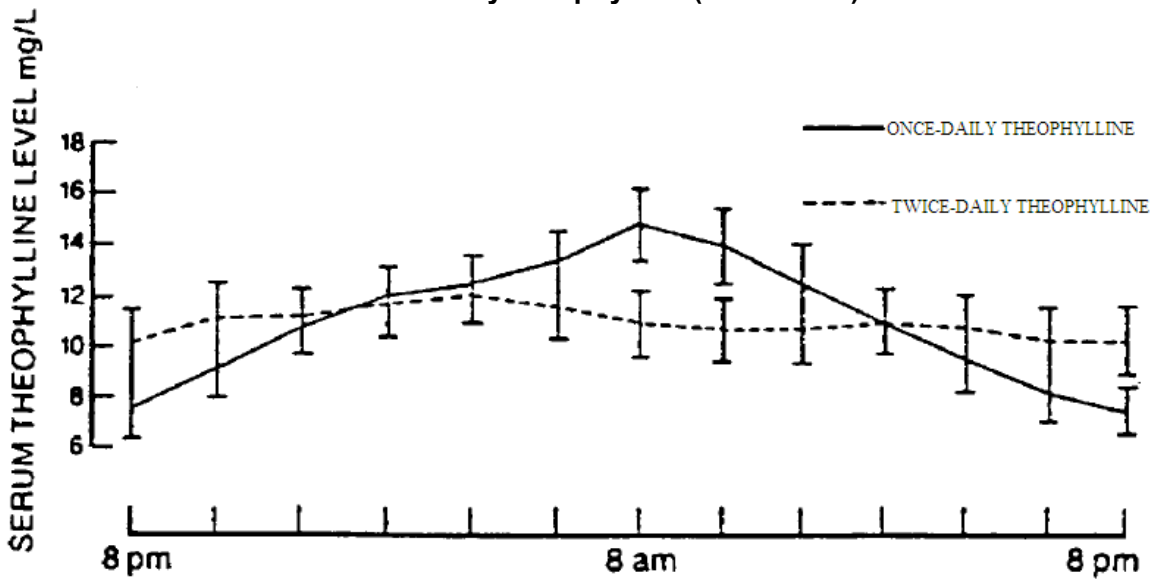
In comparing treatments, morning FEV_1 and peak expiratory flow rates were significantly higher during once-daily evening administration of theophylline than during twice-daily theophylline. There were no statistically significant differences in evening FEV_1 and PEFR values between the two treatments.

Asthma symptom scores were significantly lower during once-daily theophylline as shown in the following table.

Mean ± SEM Symptom Scores During Once-Daily Theophylline and Twice-Daily Theophylline

Symptom	Once-Daily Theophylline Treatment	Twice-Daily Theophylline Treatment	p Value (between treatments)
Dyspnea			
Daytime	0.77 ± 0.2	1.22 ± 0.3	0.045
Nighttime	0.63 ± 0.2	1.14 ± 0.3	0.003
Wheeze			
Daytime	0.63 ± 0.2	1.00 ± 0.3	0.036
Nighttime	0.62 ± 0.2	0.98 ± 0.3	0.002
Cough			
Daytime	0.29 ± 0.2	0.52 ± 0.2	0.033
Nighttime	0.31 ± 0.2	0.53 ± 0.2	NS

The investigators concluded that once-daily theophylline resulted in better control of nighttime symptoms without an increase in daytime symptoms or significant side effects and that optimal timing of theophylline dosing is an important consideration in the management of asthma.
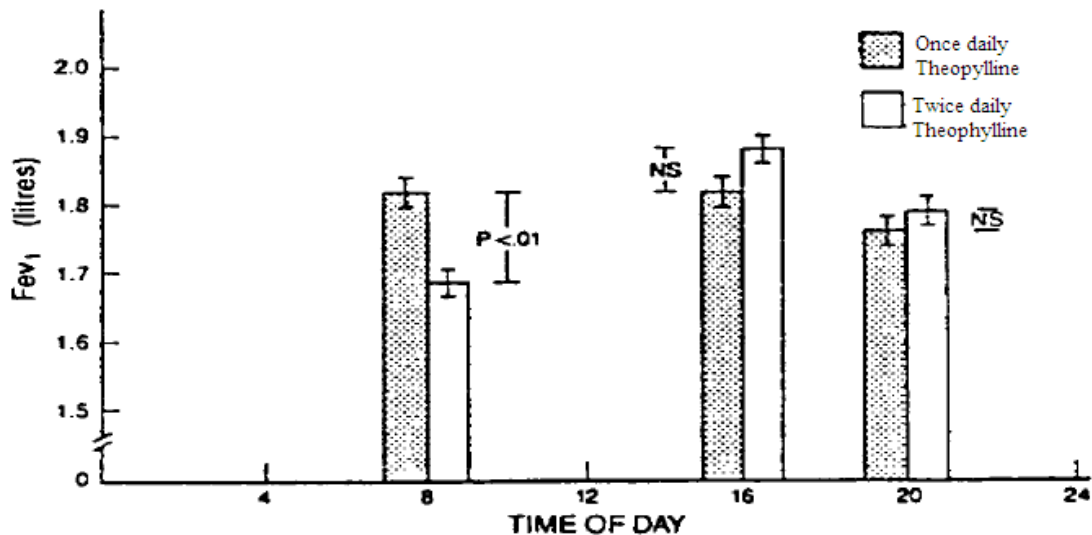
Clinical Comparison to Twice-Daily Theophylline:

In a separate double-blind, two-phase, crossover trial, 22 adult asthmatics received 7 days therapy with once-daily theophylline (dosing was at 2000h) and twice-daily theophylline (dosing was at 0800h and 2000h). For each patient the total daily theophylline dose was the same during both treatments. Asthma symptoms, drug side effects and PEFR were recorded at 0800h, 1600h, and 2000h each day. On the last 3 days of each treatment, serum theophylline and spirometry were measured at 0800h, 1600h, and 2000h.

Once daily theophylline produced greater "peak" and lower "trough" theophylline levels than did twice daily theophylline, although both drugs maintained levels within an acceptable therapeutic range.

In contrast to the theophylline level results, once daily therapy was associated with less fluctuation in pulmonary function throughout the day (see figure below), and significantly lower symptom scores for wheeze. Both dosing therapies were well tolerated and only minimal side effects were reported during the trial. The investigator concluded that once-daily theophylline produced greater stabilization of the asthmatic patients' airway function than the twice-daily formulation.

Mean ± SEM FEV$_1$ over Three Consecutive Days In 22 Adult Asthmatics During Once-Daily theophylline and Twice Daily theophylline


Effect of Morning vs Evening Dosing on Theophylline Bioavailability and Clinical Efficacy:

A double-blind, two-phase crossover trial compared the pharmacokinetics and clinical efficacy of morning vs. evening dosing with once-daily theophylline in 17 asthmatic patients. After a pre-study titration phase, patients were randomly allocated to receive active once daily theophylline at either 0800h or 2200h, with an identical placebo taken at the opposite dosing time. Symptoms and side effects were recorded in a daily diary and, after a minimum of 5 days dosing, blood samples for theophylline analyses were obtained every 2 hours for 40 consecutive hours. During the 40 hour period, spirometry was performed at 0800h. 1400h, 2200h and 0400h of the subsequent day. Patients then crossed-over to the opposite dosing time and repeated the protocol.

There were no statistically significant differences in any of the pharmacologic parameters between morning and evening dosing.

Mean ± SEM Steady-State Serum Theophylline Profiles After Once-Daily Theophylline
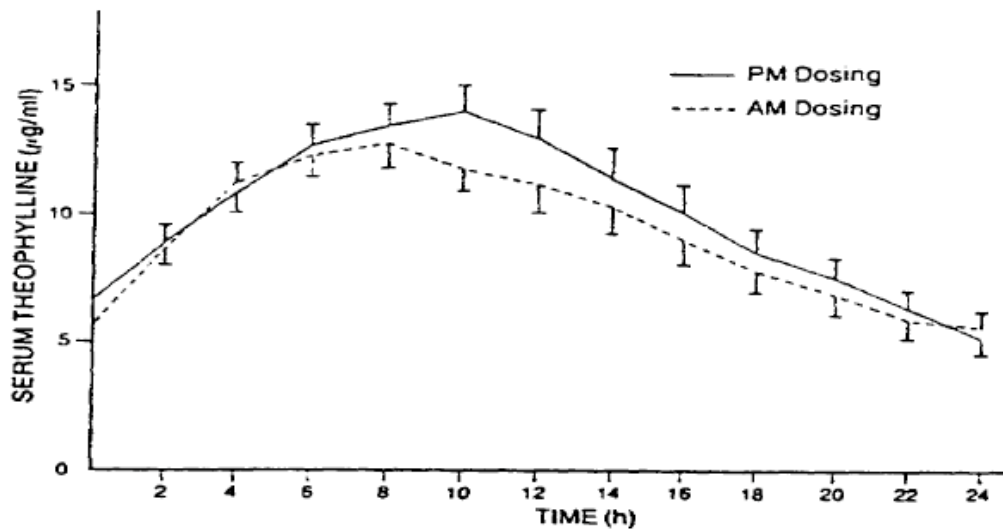
**Mean ± SEM Pharmacokinetic Parameters During
Morning and Evening Dosing with Once-Daily Theophylline**

	Morning Dosing	Evening Dosing
Cmax (mg/L)	14.5 ± 1.0	16.3 ± 1.1
Cmin	5.5 ± 0.7	5.0 ± 0.6
Tmax	8.1 ± 0.9	10.1 ± 1.0
AUC	235.5 ±18.7	256.0 ± 19.6

Evening dosing, but not morning dosing, resulted in a significant attenuation of the early morning dip in pulmonary function. FEV_1 (expressed as percent of daily best) demonstrated that significantly better spirometric responses occurred at 0400h and 0800h during evening dosing.

Also, the early morning symptoms of wheezing, chest tightness and shortness of breath were significantly lower during evening dosing. The spirometric and symptomatic benefits of evening dosing were clearly perceived by the patients, and all of the patients who continued theophylline post-study selected evening dosing.
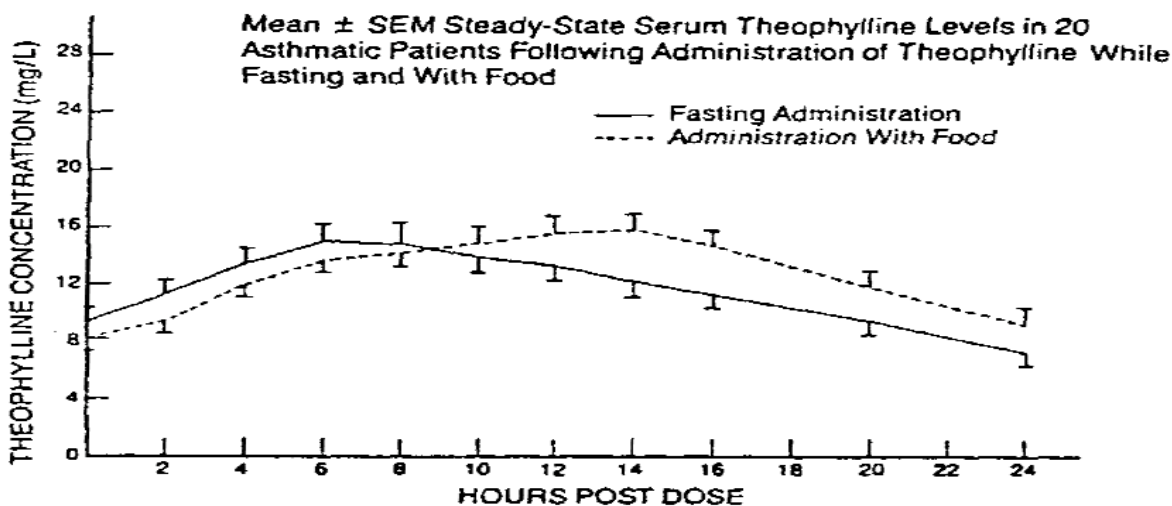
Effect of Food on Theophylline Bioavailability:

Multi-Dose Study

In a four-way crossover trial, the effect of a high-fat, high calorie meal on theophylline's bioavailability and pharmacokinetics was assessed in 20 adult asthmatics. After a minimum of 5 days continuous dosing (at 1800h), all patients received a theophylline dose under specified fasting conditions and serum theophylline levels were measured every 2 hours for 24 hours. The patient's next theophylline dose was given immediately following ingestion of a standardized high-calorie (2040), high fat (115 g) meal and theophylline levels were again measured over 24 hours. A week later the trial was repeated in the opposite sequence (i.e., dosing with food preceded fasting dosing).

The results were (Mean ± SD):

	Fasted	With Food	p Value
AUC (mg.L/ hr)	284 ± 93	313 ± 85	<0.01
Cmax (mg/L)	16.5 ±4.5	17.5 ± 4.5	NS
Tmax (hours)	8.5 ± 4.6	11.4 ± 3.6	<0.01
Cmin (mg/L)	7.0 ±3.0	7.7 ±3.1	<0.01

The overall mean serum theophylline vs. time profiles are shown below:

Mean ± SEM Steady-State Serum Theophylline Levels in 20 Asthmatic Patients Following Administration of Theophylline While Fasting and With Food

Single-Dose Study

In a three-way, randomized crossover study, 12 subjects received single doses of:

i.   three 200 mg plain aminophylline tablets (total theophylline dose 480 mg) under fasting conditions;

ii.   two 400 mg theophylline tablets under fasting conditions;

iii. two 400 mg theophylline tablets immediately following ingestion of a high-fat breakfast.

All doses were administered in the morning and, following dosing, serum theophylline levels were repeatedly measured up to 72 hours post-dose.

The results from the plain aminophylline tablets were used to calculate each subjects theophylline disposition parameters and serve as a bioavailability reference.

Marked differences in theophylline's pharmacokinetics and bioavailability were observed between food and fasting administration as shown in the following table (Mean ± SD):

	Fasted	**With Food**	**p Value**
AUC (mg.L/hr)	100 ± 51	179 ± 67	<0.001
Cmax (mg/L)	4.5 ± 0.9	8.6 ± 2.7	<0.05
Tmax (hours)	5.5 ± 1.7	12.0 ± 4.0	<0.01
Fraction absorbed (%)	53 ± 23	96 ± 46	<0.05

### Comparison Between the Multi-Dose and Single-Dose Studies

The results of the two studies are not consistent in respect of the bioavailability of theophylline when taken in the fasting state. In the multi-dose study, the mean fasting AUC was 91% of the food AUC whereas in the single dose study the fasting AUC was only 56% of the food AUC. The reasons for these differences are not known but may relate to differences in the pre-dosing fasting periods between the two studies. In the single-dose study, subjects fasted overnight for a minimum of 10 hours whereas in the multi-dose study, the patients fasted for six hours, beginning at noon.

Both studies indicate that theophylline is more completely absorbed when taken with food. Therefore, until further information concerning the effects of prolonged fasting on theophylline bioavailability is known, it is recommended that theophylline be taken within 1-2 hours of mealtime.

Monitoring Serum Theophylline Levels:

When theophylline is taken in the evening with food, the time that peak levels most frequently occur (under steady-state conditions) is 12 hours post-dose. Therefore, under such dosing conditions, 12 hours post-dose is the optimal time to measure the theophylline level in order to estimate the actual peak level. However, for patients whose actual peak level occurs at times other than 12 hours post-dose, the 12 hour level will somewhat underestimate the actual peak.

The following figure shows the distribution of the difference between the serum theophylline level measured at 12 hours post-dose and the actual peak level observed in a series of 91 steady-state serum theophylline vs. time profiles.

12 HOUR LEVEL vs. ACTUAL PEAK
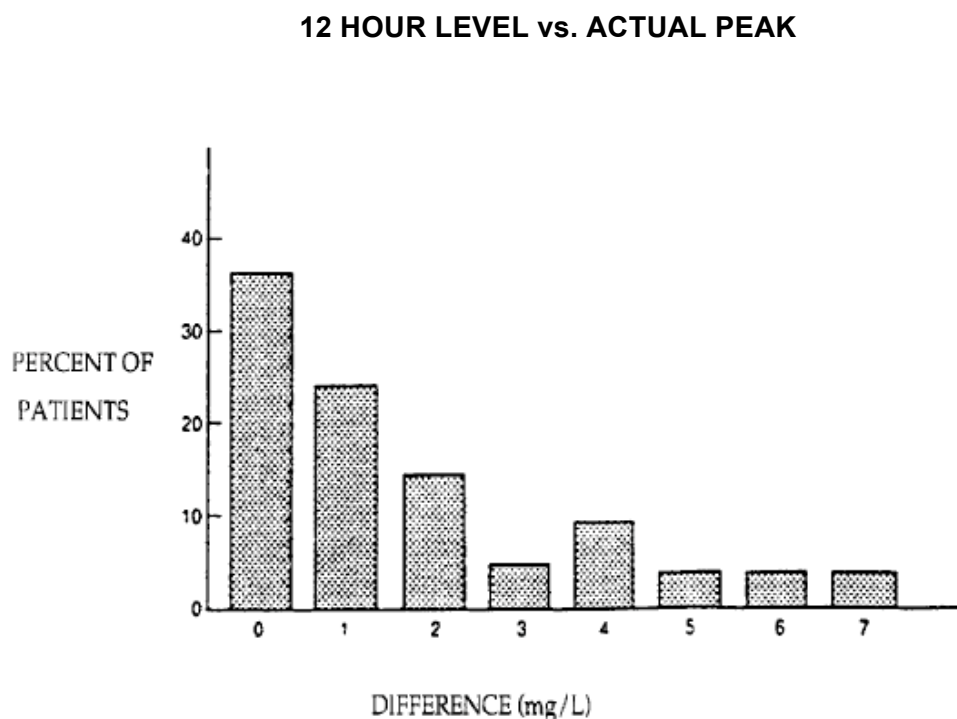
Thus, while 90% of the 12 hour levels were within 4 mg/L of the actual peak level, the possibility that an isolated 12 hour post-dose level may significantly underestimate the patient's actual peak theophylline level should always be considered.

When theophylline tablets are taken in the morning, or in the evening under fasting conditions, the time that peak levels most frequently occur is 8 hours post-dose.

Trough levels almost always occur at the time of dosing (i.e., 24 hours post-dose).

Clinical Studies

Comparative Bioavailability

Pursuant to current requirements, a comparative biostudy was conducted, under steady state fasting conditions, between Nov.24/05 – Dec.6/05, under fasting conditions, between Mar.25/06 – Apr.19/06, and under fed conditions between Aug.16/05 – Aug.28/05, using Theo ER 600mg, batch #XK379 and Uniphyl® Tablets 600mg, batch #30241. The studies consisted of randomized, double-blind, single-dose, 2-way crossover, with wash-out periods of at least 7 days. The steady state fasting study consisted of twenty-nine (29) healthy male volunteers fasting study consisted of twenty-six (26) healthy male volunteers, while the fed study consisted of thirty (30) healthy male volunteers.

The results from the bioequivalence studies indicate that Theo ER are bioequivalent to Uniphyl ® tablets. A summary containing comparative bioavailability data is provided in the following tables:

Summary Table of the Comparative Bioavailability Data Theophylline Sustained Release (Multiple 600 mg dose: 7 x 600 mg tablets) From Measured Data/Steady State Under Fasting Conditions Geometric Mean ## Arithmetic Mean (CV%)				
Parameter	Theophylline SR Tablets (AA Pharma Inc.) (Canada)	Uniphyl® Tablets (Purdue Pharma Canada)	Ratio of Geometric Means (%)##	95% Confidence Interval (%)##
AUCtau (μg•h/mL)	141.6670 145.8646 (23.50)	134.3310 137.9830 (25.84)	105.46	96.13 – 115.70
Cmax (μg/mL)	8.2980 8.5157 (21.69)	8.3830 8.5856 (23.98)	98.98	90.18 – 108.64
Cmin (μg/mL)	3.0170 3.3966 (45.63)	2.7200 2.8784 (35.45)	110.92	93.23 – 131.97
Tmax# (h)	6.2308 (40.43)	6.8077 (62.60)		
Fluc# (%)	88.0042 (30.44)	101.1665 (17.34)		
# Arithmetic mean (CV%) only. ## Based on the least squares estimate. † Uniphyl® Tablets is manufactured by Purdue Pharma, Canada, and was purchased in Canada.				

Summary Table of the Comparative Bioavailability Data Theophylline Sustained Release (A single 600 mg dose: 1 x 600 mg tablet) From Measured Data/Fasting Conditions Geometric Mean ## Arithmetic Mean (CV%)				
Parameter	Theophylline SR Tablets (AA Pharma Inc.) (Canada)	Uniphyl® Tablets (Purdue Pharma Canada)	Ratio of Geometric Means (%)##	95% Confidence Interval (%)##
AUCt (μg•h/mL)	133.778 141.2028 (32.92)	131.339 139.7591 (36.80)	101.86	88.21 – 117.61
AUCinf (μg•h/mL)	138.620 145.8721 (32.04)	136.678 144.9577 (35.91)	101.42	88.39 – 116.74
Cmax	6.580	6.625	99.31	90.65 – 108.79

Summary Table of the Comparative Bioavailability Data Theophylline Sustained Release (A single 600 mg dose: 1 x 600 mg tablet) From Measured Data/Fasting Conditions Geometric Mean ## Arithmetic Mean (CV%)				
Parameter	Theophylline SR Tablets (AA Pharma Inc.) (Canada)	Uniphyl® Tablets (Purdue Pharma Canada)	Ratio of Geometric Means (%)##	95% Confidence Interval (%)##
(µg/mL)	6.6970 (18.91)	6.8363 (25.26)		
Tmax# (h)	9.8621 (60.76)	7.2069 (60.18)		
Thalf# (h)	6.9445 (19.11)	7.8286 (23.98)		
# Arithmetic mean (CV%) only. ## Based on the least squares estimate. † Uniphyl® Tablets is manufactured by Purdue Pharma, Canada, and was purchased in Canada.				

Summary Table of the Comparative Bioavailability Data Theophylline Sustained Release (A single 600 mg dose: 1 x 600 mg tablet) From Measured Data/Fed Conditions Geometric Mean ## Arithmetic Mean (CV%)				
Parameter	Theophylline SR Tablets (AA Pharma Inc.) (Canada)	Uniphyl® Tablets (Purdue Pharma Canada)	Ratio of Geometric Means (%)##	95% Confidence Interval (%)##
AUCt (µg•h/mL)	168.036 177.6503 (33.00)	171.486 179.9892 (32.30)	97.99	86.20 – 111.38
AUCinf (µg•h/mL)	172.184 181.8155 (32.63)	175.950 184.3852 (31.79)	97.86	86.23 – 111.05
Cmax (µg/mL)	8.309 8.6243 (27.47)	8.492 8.6970 (23.95)	97.84	86.88 – 110.20
Tmax# (h)	11.7000 (47.62)	10.8000 (44.07)		
Thalf# (h)	7.1013 (28.62)	7.4830 (27.89)		
# Arithmetic mean (CV%) only. ## Based on the least squares estimate. † Uniphyl® Tablets is manufactured by Purdue Pharma, Canada, and was purchased in Canada.				

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 incidence of adverse reactions increases at serum concentrations over 15 mg/L (82.5 µmol/L). Levels in excess of (20 mg/L) 110 µmol/L are usually quite toxic in most patients, although a few patients can tolerate higher levels without significant side-effects. Tolerance to some of the toxic effects of theophylline is known to occur.

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