PRODUCT MONOGRAPH

Pr THEO ER

Theophylline sustained release tablets

House Standard

400 mg and 600 mg

BRONCHODILATOR

AA Pharma Inc.
1165 Creditstone Road, Unit #1
Vaughan, Ontario
L4K 4N7

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PRODUCT MONOGRAPH

NAME OF DRUG

Pr THEO ER

(theophylline sustained release 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 pharmacokinetic 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 60% 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% and 1-methylxanthine is excreted in smaller amounts.

The generally accepted optimal therapeutic serum theophylline concentrations are 5 to 15 mg/L (27.5 to 82.5 mcmol/L). Levels above 20 mg/L (110 mcmol /L) are usually associated with significant adverse drug reactions. The pharmacokinetics of theophylline are influenced by a number of variables such as age, body weight, diet, 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

THEO ER (theophylline sustained release tablets) is indicated for the symptomatic treatment of reversible bronchoconstriction associated with bronchial asthma, chronic obstructive pulmonary emphysema, chronic bronchitis and related bronchospastic disorders.

THEO ER is not recommended for use in children under 12 years of age.

CONTRAINDICATIONS

Theo ER (theophylline sustained release tablets) should not be administered to patients with:

- hypersensitivity to theophylline, xanthines derivatives, or the excipients used in these drug products
- coronary artery disease (where cardiac stimulation might prove harmful)
- peptic ulcers
- concomitant use with ephedrine in children

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 mcmol/L) and levels above 20 mg/L (110 mcmol/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:
Due to potential decreased theophylline clearance, which may result in increased serum levels and significant adverse drug reactions in patients, dose reduction and monitoring of serum theophylline concentrations may be required in elderly patients and in patients:

- with impaired liver or kidney function
- over 55 years of age, particularly males and those with chronic lung disease
- with cardiac disease
- with active influenza or other viral disease or after influenza immunization
- with a high carbohydrate, low protein diet
- with hypothyroidism (and when starting acute treatment for hypothyroidism)
- with a sustained high fever

Due to potential increased theophylline 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.

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

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

Theophylline may exacerbate frequency and duration of seizures and therefore caution should be exercised in patients with history of seizures.

Drug Interactions:

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

Drug	Effect on Theophylline Clearance and Elimination Half-life following co-administration	Clinical Comments
Acyclovir, allopurinol, carbimazole, cimetidine, diltiazem, disulfiram, fluconazole, interferon, isoniazid, quinolone antibiotics (e.g., ciprofloxacin), macrolide antibiotics (e.g., erythromycin, clarithromycin, troleandomycin), methotrexate, mexiletine, nizatidine, oral contraceptives, propafenone, propranolol, pentoxiphylline, selective serotonin re-uptake inhibitors (e.g., fluvoxamine), terbinafine*, thiabendazole, verapamil	↑ $t_{½}$, ↓ clearance	It may be necessary to reduce the dosage of theophylline to avoid adverse drug reactions. Monitoring of serum theophylline concentrations may be required. The concomitant use of theophylline and fluvoxamine should usually be avoided.
Alkalinizing agents	↑ $t_{½}$, ↓ clearance	It may be necessary to reduce the dosage of theophylline to avoid adverse drug reactions. Monitoring of serum theophylline concentrations may be required.
Treatments associated with hypothyroidism	↑ $t_{½}$, ↓ clearance	It may be necessary to reduce the dosage of theophylline to avoid adverse drug reactions. Monitoring of serum theophylline concentrations may be required.
Treatments associated with hyperthyroidism	↓ $t_{½}$, ↑ clearance	It may be necessary to increase the dosage of theophylline to ensure therapeutic effect.

Drug	Effect on Theophylline Clearance and Elimination Half-life following co-administration	Clinical Comments
		Monitoring of serum theophylline concentrations may be required.
Influenza vaccine	↑ $t_{½}$, clearance reported to be decreased or no change	
Aminoglutethimide, barbiturates, carbamazepine, hypericum perforatum (St. John's Wort), isoproterenol, phenytoin, rifampin, ritonavir, sulfinpyrazone	↓ $t_{½}$, ↑ clearance	It may be necessary to increase the dosage of theophylline to ensure therapeutic effect. Monitoring of serum theophylline concentrations may be required.
Tobacco, alcohol	↓ $t_{½}$, ↑ clearance	
Acidifying agents	↓ $t_{½}$, ↑ clearance	

*Additional information provided in paragraphs below

Effect of Terbinafine on the Pharmacokinetics of Theophylline

Single dose terbinafine did not significantly alter the pharmacokinetics of theophylline in a randomized, open-label, single-dose, three-period crossover study, in healthy male and female adult subjects (n = 18) treated orally with 250 mg terbinafine, 375 mg theophylline, and 250 mg terbinafine plus 375 mg theophylline.

Multiple dose terbinafine increased the AUC and half-life of theophylline by 16% and 24%, respectively, and decreased the oral clearance of theophylline by 14%, in a randomized, open label, two-period crossover study in healthy male and female adult subjects (n = 12) treated orally with a single dose of 5 mg/kg theophylline alone (mean 345 mg, range 307 to 397 mg) and 2 hours after the last of 4 daily doses of 250 mg terbinafine.

Effect of Theophylline on the Pharmacokinetics of Terbinafine

Theophylline increased the C_{max} and AUC of terbinafine by 25% each, and decreased the oral clearance of terbinafine by 24% in a randomized, open-label, single-dose, three-period crossover study, in healthy male and female adult subjects (N = 18) treated orally with 250 mg terbinafine, 375 mg theophylline, and 250 mg terbinafine plus 375 mg theophylline.

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

Drug	Influence of Theophylline	
Adenosine receptor agonists	Inhibits the effect of adenosine receptor agonists	Caution with concomitant use
Benzodiazepines	Opposes the sedatory effects	Caution with concomitant use
Digitalis glycosides	↑ cardiac effect	Caution with concomitant use
Halothane	Occurrence of arrhythmias	Caution with concomitant use
Thiazides	↑ diuresis	Caution with concomitant use
Nephrotoxic drugs	↑ nephrotoxicity	Caution with concomitant use
Lithium	↑ ratio of lithium/creatinine clearance, thus a decrease in serum lithium levels	Caution with concomitant use
Lomustine	Results in thrombocytopenia	Caution with concomitant use
Sympathomimetic amines	↑ toxicity, ↑ CNS stimulation	Caution with concomitant use
Coumarin anticoagulants	↓ anticoagulant activity ↑ prothrombin and fibrinogen blood concentrations ↓ prothrombin time	Caution with concomitant use
Allopurinol	↓ antihyperuricemic action	Caution with concomitant use
Probenecid and pyrazolone derivatives	↓ uricosuric action	Caution with concomitant use

For COPD patients, the concomitant use of theophylline and roflumilast should usually be avoided.

Care should be taken with concomitant use of 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 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 potassium 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. THEO ER should not be administered during pregnancy unless considered essential by the physician. Theophylline should be given to pregnant women or nursing mothers only when the anticipated benefits outweigh the risk to the child.

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 classified by body system include:

Gastrointestinal:	Abdominal pain, anorexia, diarrhea, epigastric pain, gastroesophageal reflux, hematemesis, intestinal bleeding, nausea, reactivation of peptic ulcer and vomiting
Central Nervous System:	Convulsions, dizziness, headache, irritability, reflex hyperexcitability, restlessness, twitching and tremors
Cardiovascular:	Atrial tachycardia, circulatory failure, extrasystoles, flushing, hypotension, palpitations, sinus tachycardia and ventricular arrhythmias
Skin and Subcutaneous:	Pruritus and rash
Immune:	Anaphylactic reaction, anaphylactoid reaction and hypersensitivity
Metabolic and Nutritional:	Hyperuricemia, hyperglycemia
Psychiatric:	Agitation, anxiety, insomnia, sleep disorder
Renal:	Albuminuria, diuresis, hematuria and urinary retention (see **PRECAUTIONS**, Patients with Special Diseases and Conditions)
Others:	Tachypnea and inappropriate ADH syndrome

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms of acute theophylline toxicity: Theophylline has a low therapeutic index. Theophylline toxicity is most likely to occur when serum concentrations exceed 20 mcg/mL (110 mcmol/L) and becomes progressively more severe at higher serum concentrations.

Symptoms:

Alimentary symptoms:	Nausea, vomiting, abdominal pain and hematemesis
Cardiovascular symptoms:	Sinus tachycardia, ventricular arrthymias and hypotension
Metabolic symptoms:	Hyperglycemia, hypokalemia, acid/base disturbance and rhabdomyolysis
Neurological symptoms:	Restlessness, convulsion, seizure and coma in severe cases

Treat symptoms on appearance, which may include hypokalemia, supraventricular and ventricular arrhythmias, convulsions and seizures. Sustained release tablets may release medication for hours, facilitated by formation of tablet aggregates, or bezoars, in the stomach. 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) Administration of oral activated charcoal has been found to reduce high theophylline serum concentrations. Multiple doses of activated charcoal should be also considered. Seizure prophylaxis may be indicated for certain patients.

2) Administration of a cathartic can be considered in addition to oral activated charcoal. Repeated doses of cathartic are not recommended due to possible adverse effects.

3) In severe poisoning or cases where gastric decontamination is not feasible, extracorporeal removal (i.e., hemodialysis, charcoal-column hemoperfusion) can be employed.

C. If patient is having a seizure:

1) Establish an airway.

2) Administer oxygen.

3) Intravenous benzodiazepines are generally considered as first line therapy although some benzodiazepines may have reduced efficacy in theophylline overdose due to suspected pharmacodynamics interactions. Second line agents should be used if resistant, although phenytoin should be avoided.

4) Continue to provide full supportive care and monitoring.

D. Post Seizure Coma:

1) Maintain airway and oxygenation.

2) Consider the recommendations (B above, steps 1 to 3) to prevent absorption of the drug. Note that an unprotected airway is a contraindication to activated charcoal administration due to concerns of aspiration.

3) Continue to provide full supportive care and monitoring.

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 5 and 15 mg/L (27.5 to 82.5 mcmol/L). Theophylline distributes poorly into body fat, therefore, mg/kg doses should be calculated on the basis of lean body mass (ideal body weight). A serum level of 5 mcg/mL (27.5 mcmol/L) represents the lower level of clinical effectiveness. Whereas the serum level of 20 mg/L (110 mcmol/L) is an important reference point in terms of toxicity (See **Precautions**).

Monitoring of plasma theophylline concentrations may be required when:

- higher doses are prescribed
- patients have co-morbidities resulting in impaired clearance (see **PRECAUTIONS, Patients with Special Diseases and Conditions**)
- theophylline is co-administered with medication that reduces theophylline clearance (see **PRECAUTIONS, Drug Interactions**)

Initial Adult Dose: For patients not currently receiving oral theophylline, the recommended initial dose is 400 to 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 theophylline tablets be taken with food, or within 1 to 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.

It is not possible to ensure interchangeability between different sustained release theophylline products. Once titrated to an effective dose, patients should not be changed from one sustained release theophylline product to another sustained release xanthine preparation without re-titration and careful clinical monitoring.

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 5 to 15 mg/L (27.5 to 82.5 mcmol/L), although some patients obtain a very good bronchodilator effect from serum levels less than 10 mg/L (55 mcmol/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 must be swallowed whole and should not be broken, 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°C to 30°C.

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

INFORMATION FOR THE CONSUMER

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 administered to patients with:

- hypersensitivity to xanthines
- an allergy to theophylline or the excipients used in the drug product
- heart disease
- peptic ulcers
- concomitant use with ephedrine in children

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)
- have a continuous high fever
- have cystic fibrosis

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:

- acyclovir, adenosine receptor agonists, aminoglutethimide, antibiotics, ephedrine, fluconazole, glucagon, halothane, interferons, lithium, lomustine, methotrexate, oral contraceptives, terbinafine or 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)
- selective serotonin re-uptake inhibitors, e.g., fluvoxamine (drugs used to treat depression)
- ritonavir (used to treat HIV infection)
- roflumilast (used in patients with COPD). The concurrent use of this medication should be avoided

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 not 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** break, **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 or develop a rash and itching. Occasionally, convulsions (fits) have been reported. If any of these problems bother you or you have any other problems, please contact your doctor immediately.

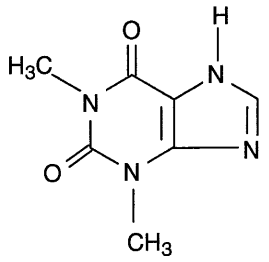
Severe allergic reactions can occur while taking THEO ER. If you develop a rash, hives, swelling of the face, lips, tongue or throat, have difficulty swallowing or breathing, stop taking THEO ER and seek immediate emergency medical help.

Overdose

In the case of a drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

CHEMISTRY

Structure:



Chemical Name: 1,3 Dimethylxanthine

Molecular Weight: 180.2 (anhydrous) g/mol
198.2 (monohydrate) g/mol

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 60% bound to plasma proteins at the therapeutic plasma concentration range of 5 to 15 mg/L (27.5 to 82.5 mcmol/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 to 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 mean elimination half-life associated with theophylline is approximately 7 hours.

The enzymes responsible for theophylline metabolism are unknown but do not include xanthine oxidase.

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.

BIOAVAILABILITY AND CLINICAL DATA

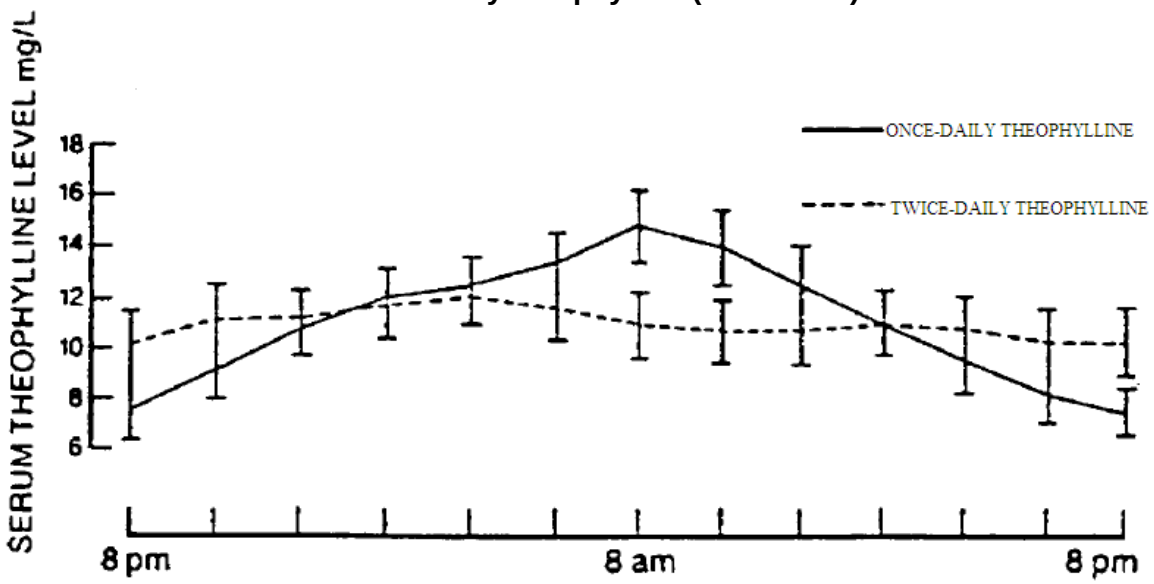
Bioavailability and Clinical Comparison to Twice-Daily Theophylline:

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	**C_{max}** mg/L	**C_{min}** mg/L	**T_{max}** hours	**AUC** mg.hr/L
Once daily theophylline	783	15.9	6.5	11.3	271
	±57	±4.5	±3.1	±3.3	±98
Twice daily theophylline	766	13.4	8.7	6.8	263
	±115	±4.8	±4.4	±3.8	±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.

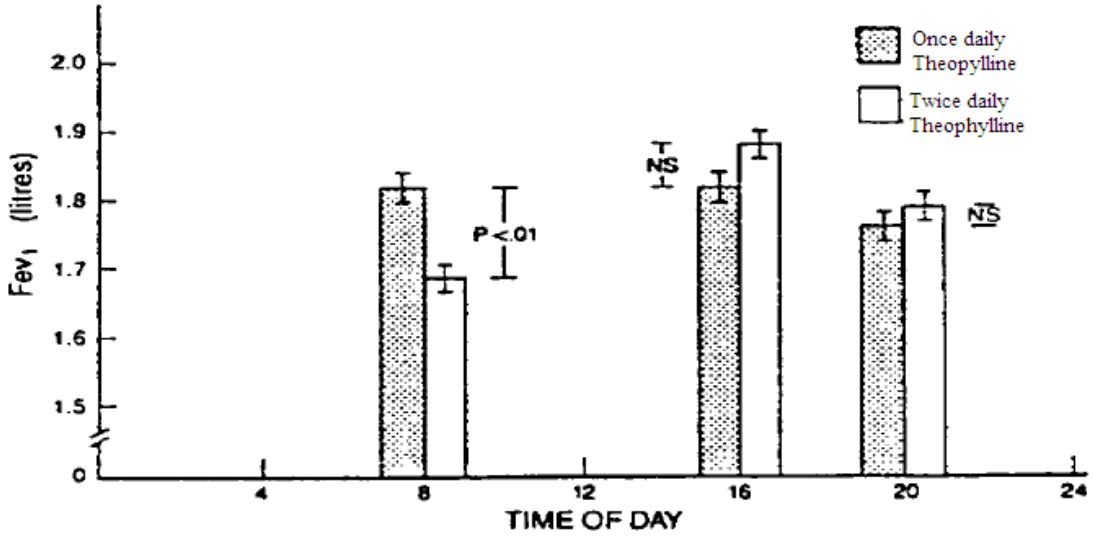
Clinical Comparison to Twice-Daily Theophylline:

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



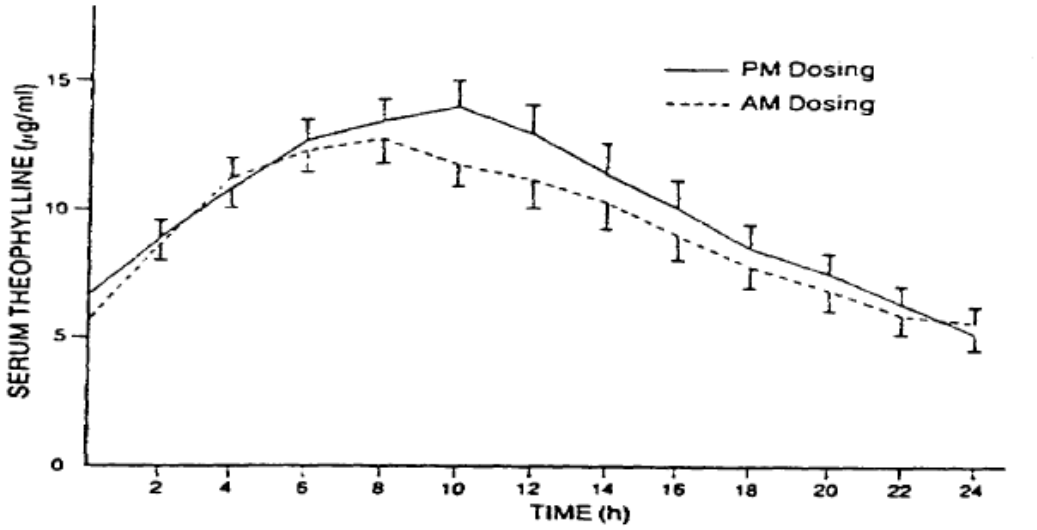
Effect of Morning vs Evening Dosing on Theophylline Bioavailability and Clinical Efficacy:

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
C_{max} (mg/L)	14.5 ± 1.0	16.3 ± 1.1
C_{min}	5.5 ± 0.7	5.0 ± 0.6
T_{max}	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.

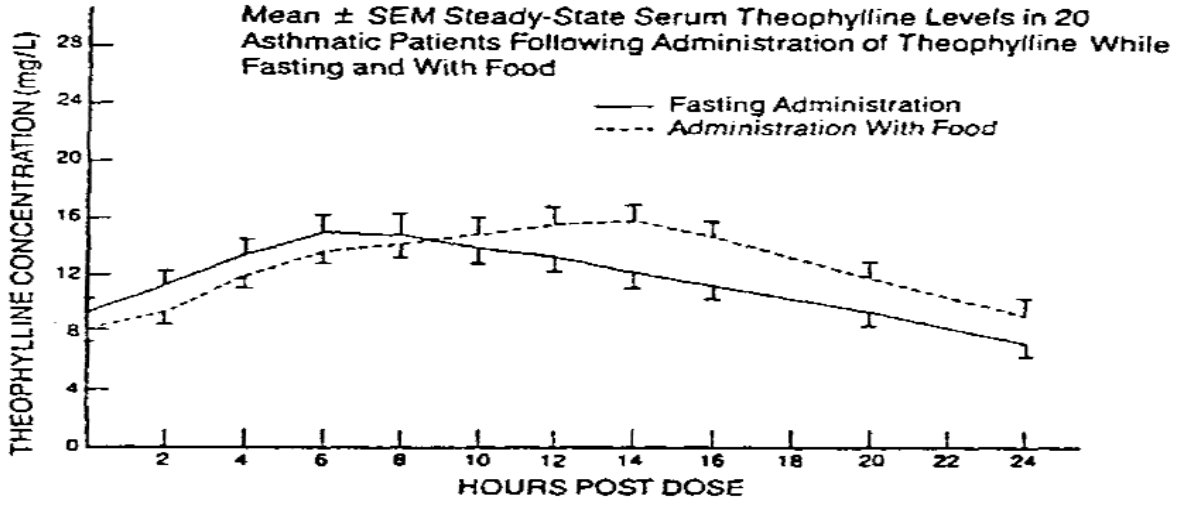
Also, the early morning symptoms of wheezing, chest tightness and shortness of breath were significantly lower during evening dosing. The spirometric and symptomatic benefits of evening dosing were clearly perceived by the patients, and all of the patients who continued theophylline post-study selected 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.hr/L)	284 ± 93	313 ± 85	<0.01
C_{max} (mg/L)	16.5 ±4.5	17.5 ± 4.5	NS
T_{max} (hours)	8.5 ± 4.6	11.4 ± 3.6	<0.01
C_{min} (mg/L)	7.0 ±3.0	7.7 ±3.1	<0.01

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



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.hr/L)	100 ± 51	179 ± 67	<0.001
C_{max} (mg/L)	4.5 ± 0.9	8.6 ± 2.7	<0.05
T_{max} (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.

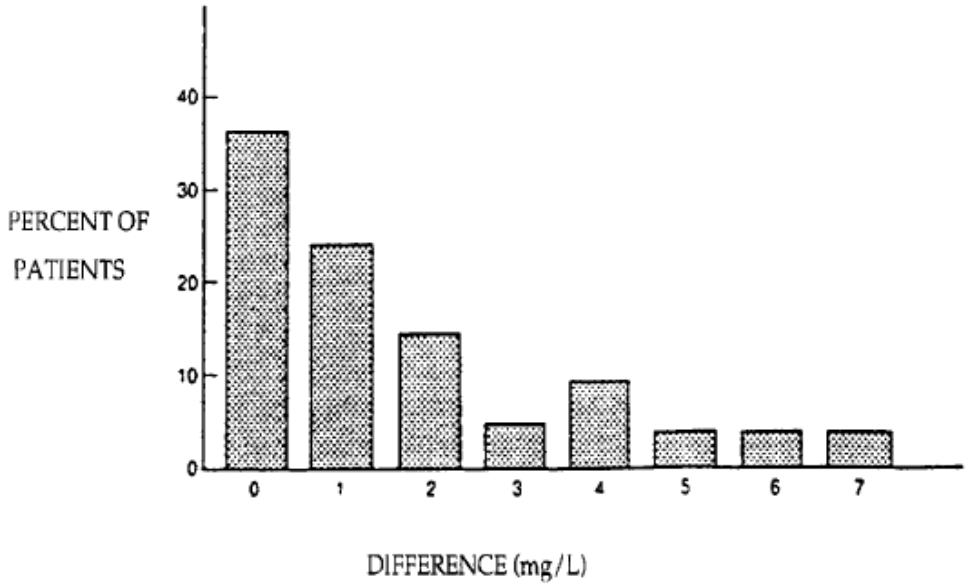
Both studies indicate that theophylline is more completely absorbed when taken with food. Therefore, until further information concerning the effects of prolonged fasting on theophylline bioavailability is known, it is recommended that theophylline be taken within 1 to 2 hours of mealtime.

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 (%)##
AUC_{tau} (mcg•h/mL)	141.6670 145.8646 (23.50)	134.3310 137.9830 (25.84)	105.46	96.13 – 115.70
C_{max} (mcg/mL)	8.2980 8.5157 (21.69)	8.3830 8.5856 (23.98)	98.98	90.18 – 108.64
C_{min} (mcg/mL)	3.0170 3.3966 (45.63)	2.7200 2.8784 (35.45)	110.92	93.23 – 131.97
T_{max}# (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 (%)##
AUC_t (mcg•h/mL)	133.778 141.2028 (32.92)	131.339 139.7591 (36.80)	101.86	88.21 – 117.61
AUC_{inf} (mcg•h/mL)	138.620 145.8721 (32.04)	136.678 144.9577 (35.91)	101.42	88.39 – 116.74
C_{max} (mcg/mL)	6.580 6.6970 (18.91)	6.625 6.8363 (25.26)	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 (%)##
T_{max} # (h)	9.8621 (60.76)	7.2069 (60.18)		
T_{half} # (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 (%)##
AUC_t (mcg•h/mL)	168.036 177.6503 (33.00)	171.486 179.9892 (32.30)	97.99	86.20 – 111.38
AUC_{inf} (mcg•h/mL)	172.184 181.8155 (32.63)	175.950 184.3852 (31.79)	97.86	86.23 – 111.05
C_{max} (mcg/mL)	8.309 8.6243 (27.47)	8.492 8.6970 (23.95)	97.84	86.88 – 110.20
T_{max} # (h)	11.7000 (47.62)	10.8000 (44.07)		
T_{half} # (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 mcmol/L). Levels in excess of (20 mg/L) 110 mcmol/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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