SENOPHYLLINE - theophylline anhydrous, choline
Physician Therapeutics LLC

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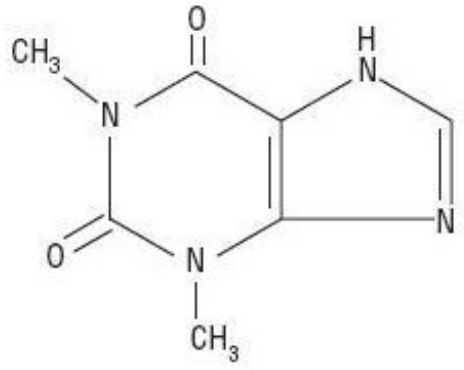
Senophylline

DESCRIPTION

Theophylline is structurally classified as a methylxanthine. It occurs as a white, odorless, crystalline powder with a bitter taste. Anhydrous theophylline has the chemical name 1H-Purine-2,6-dione,3,7-dihydro-1,3-dimethyl-, and is represented by the following structural formula:



$C_7H_8N_4O_2$ M.W. 180.17

This product allows a 12-hour dosing interval for a majority of patients and a 24-hour dosing interval for selected patients (see DOSAGE AND ADMINISTRATION section for description of appropriate patient populations).

Each extended-release tablet for oral administration contains either 100 mg, 200 mg, 300 mg or 450 mg of anhydrous theophylline. Tablets also contain as inactive ingredients: hypromellose, anhydrous lactose, magnesium stearate and povidone.

CLINICAL PHARMACOLOGY

Mechanism of Action

Theophylline has two distinct actions in the airways of patients with reversible obstruction; smooth muscle relaxation (i.e., bronchodilation) and suppression of the response of the airways to stimuli (i.e., non-bronchodilator prophylactic effects). While the mechanisms of action of theophylline are not known with certainty, studies in animals suggest that bronchodilatation is mediated by the inhibition of two isozymes of phosphodiesterase (PDE lll and, to a lesser extent, PDE IV) while non-bronchodilator prophylactic actions are probably mediated through one or more different molecular mechanisms, that do not involve inhibition of PDE lll or antagonism of adenosine receptors. Some of the adverse effects associated with theophylline appear to be mediated by inhibition of PDE lll (e.g., hypotension, tachycardia, headache, and emesis) and adenosine receptor antagonism (e.g., alterations in cerebral blood flow).

Theophylline increases the force of contraction of diaphragmatic muscles. This action appears to be due to enhancement of calcium uptake through an adenosine-mediated channel.

Serum Concentration-Effect Relationship

Bronchodilation occurs over the serum theophylline concentration range of 5 to 20 mcg/mL. Clinically important improvement in symptom control has been found in most studies to require peak serum theophylline concentrations greater than 10 mcg/mL, but patients with mild disease may benefit from lower concentrations. At serum theophylline concentrations greater than 20 mcg/mL, both the frequency and severity of adverse reactions increase. In general, maintaining peak serum theophylline concentrations between 10 and 15 mcg/mL will achieve most of the drug's potential therapeutic benefit while minimizing the risk of serious adverse events.

Pharmacokinetics

Overview

Theophylline is rapidly and completely absorbed after oral administration in solution or immediate-release solid oral dosage form. Theophylline does not undergo any appreciable pre-systemic elimination, distributes freely into fat-free tissues and is extensively metabolized in the liver.

The pharmacokinetics of theophylline vary widely among similar patients and cannot be predicted by age, sex, body weight or other demographic characteristics. In addition, certain concurrent illnesses and alterations in normal physiology (see Table I) and co-administration of other drugs (see Table II) can significantly alter the pharmacokinetic characteristics of theophylline. Within-subject variability in metabolism has also been reported in some studies, especially in acutely ill patients. It is, therefore, recommended that serum theophylline concentrations be measured frequently in acutely ill patients (e.g., at 24-hr intervals) and periodically in patients receiving long-term therapy, e.g., at 6 to 12 month intervals. More frequent measurements should be made in the presence of any condition that may significantly alter theophylline clearance (see PRECAUTIONS, Laboratory Tests).

Table I. Mean and range of total body clearance and half-life of theophylline related to age and altered physiological states.*

Population Characteristics Age	Total body clearance† mean (range)‡ (mL/kg/min)	Half-life mean (range)‡ (hr)
Premature neonates postnatal age 3-15 days postnatal age 25-57 days	0.29(0.09-0.49) 0.64(0.04-1.2)	30(17-43) 20(9.4-30.6)
Term infants postnatal age 1-2 postnatal age 3-30 weeks	NR§ NR§	25.7(25-26.5) 11(6-29)
Children 1-4 years 4-12 years 13-15 years 6-17 years	1.7(0.5-2.9) 1.6(0.8-2.4) 0.9(0.48-1.3)	3.4(1.2-5.6) NR§ NR§ 2.7(1.5

6-17 years	1.4(0.2-2.6)	3.7(1.5-5.9)
Adults (16-60 years) otherwise healthy non-smoking asthmatics	0.65(0.27-1.03)	8.7(6.1-12.8)
Elderly (>60 years) non-smokers with normal cardiac, liver, and renal function	0.41(0.21-0.61)	9.8(1.6-18)
Concurrent illness or altered physiological state		
Acute pulmonary edema	0.33¶(0.07-2.45)	19¶(3.1-82)
COPD->60 years, stable non-smoker > 1 year	0.54(0.44-0.64)	11(9.4-12.6)
COPD with cor pulmonale	0.48(0.08-0.88)	NR§
Cystic fibrosis (14-28 years)	1.25(0.31-2.2)	6.0(1.8-10.2)
Fever associated with acute viral respiratory illness(children 9-15 years)	NR§	7.0(1.0-13)
Liver disease cirrhosis	0.31¶(0.1-0.7)	32¶(10-56)
acute hepatitis	0.35(0.25-0.45)	19.2(16.6-21.8)
cholestasis	0.65(0.25-1.45)	14.4(5.7-31.8)
Pregnancy 1st trimester	NR§	8.5(3.1-13.9)
2nd trimester	NR§	8.8(3.8-13.8)
3rd trimester	NR§	13.0(8.4-17.6)
Sepsis with multi-organ failure	0.47(0.19-1.9)	18.8(6.3-24.1)
Thyroid disease - hypothyroid	0.38(0.13-0.57)	11.6(8.2-25)
Hyperthyroid	0.8(0.68-0.97)	4.5(3.7-5.6)

NOTE: In addition to the factors listed above, theophylline clearance is increased and half-life decreased by low carbohydrate/highprotein diets, parenteral nutrition, and daily consumption of charcoal-broiled beef. A high carbohydrate/low protein diet can decreasethe clearance and prolong the half-life of theophylline.		

* For various North American patient populations from literature reports. Different rates of elimination and consequent dosage requirements have been observed among other peoples.
† Clearance represents the volume of blood completely cleared of theophylline by the liver in one minute. Values listed were generally determined at serum theophylline concentrations less than 20 mcg/mL; clearance may decrease and half-life may increase at higher serum concentrations due to non-linear pharmacokinetics.
‡ Reported range or estimated range (mean +/- 2 SD) where actual range not reported.
§ NR = not reported or not reported in a comparable format.
¶ Median

Absorption

Theophylline is rapidly and completely absorbed after oral administration in solution or immediate-release solid oral dosage form. After a single dose immediate release theophylline of 5 mg/kg in adults, a mean peak serum concentration of about 10 mcg/mL (range 5 to 15 mcg/mL) can be expected 1 to 2 hours after the dose. Co-administration of theophylline with food or antacids does not cause clinically significant changes in the absorption of theophylline from immediate-release dosage forms.

Single-Dose Study

(450 mg)

A single-dose, two-way crossover study was conducted in sixteen healthy male volunteers under fasting conditions, with one 450 mg tablet being administered at 7 a.m. with a 6 oz. glass of water. No food or liquid (other than water) was allowed for 4 hours after which a standard lunch was served. Mean peak theophylline serum level (Cmax) was 6.69 mcg/mL and mean time of peak serum concentration (Tmax) was 8.31 hours.

(300 mg)

A single-dose crossover study was conducted in twelve healthy male volunteers to compare pharmacokinetic parameters when theophylline extended-release tablets were administered with and without food. Subjects were fasted overnight and received a single 300 mg tablet early the following morning.

When dosing was done under fed conditions, the subjects received a standard breakfast consisting of 2 fried eggs, 2 strips of bacon, 4 oz. hash brown potatoes, 1 slice of toast with a pat of butter, and 8 oz. whole milk 15 minutes pre-dosing. No food was allowed for five hours post-dosing, then a standard lunch was served; at ten hours post-dosing a standard supper was served. Mean peak theophylline serum levels for the two treatments were 3.7 mcg/mL (fasting) and 4.4 mcg/mL (with food). The time of peak serum level varied from subject to subject, occurring from 4 to 14 hours after dosing. However, 92% of the subjects had serum levels at least 75% of the maximum value at 4 to 8 hours after dosing, during each phase.

Thus, blood samples taken 4 to 8 hours post-dosing should reference the peak serum level for most patients. The mean Tmax was 6.2 hours (fasting) and 8.7 hours (with food). The respective AUC (0-inf.)

for these treatments were 73.3 mcg x hr/mL and 82.2 mcg x hr/mL, respectively.

Multiple-Dose Study

(300 mg)

A multiple-dose, steady-state study was conducted under fed conditions. Three high fat content meals were served at 6:30 a.m., 12 noon and 6:30 p.m. Nineteen normal subjects were dosed at 300 mg every 12 hours (7 p.m. and 7 a.m.) for eight doses. Dosing began one-half hour after the evening meal with the test dose occurring one-half hour after breakfast. At steady-state, the mean peak concentration was 8.8 mcg/mL and the mean trough concentration was 5.9 mcg/mL.

The time of peak concentration (Tmax) was 6.2 hours. The average percent fraction of fluctuation [(Cmax - Cmin/Cmin) x 100] was 49% for this formulation and dosing regimen.

The subjects used for this study exhibited a mean half-life of 8.3 hours (range 5.2 to 12.2) and a mean clearance of 3.5 L/hour (range 2.3 to 5.6) as determined in a separate single-dose clearance study using 500 mg of immediate-release theophylline, prior to this multiple-dose study.

(200 mg)

A multiple-dose, steady-state study was conducted in sixteen normal subjects, with one 200 mg tablet given every 12 hours for eight doses. Three high fat content meals were served at 6:30 a.m., 12 noon and 6:30 p.m. Dosing began one-half hour after the evening meal with the test dose occurring one-half hour after breakfast. At steady-state following the eighth dose, the mean Cmax was 5.1 mcg/mL and the mean Cmin was 3.7 mcg/mL. The mean time to peak concentration was 6.2 hours. The average percent fraction of fluctuation was 39%.

The subjects used for this study exhibited a mean half-life of 8.7 hours (range 5.0 to 14.6) and a mean clearance of 3.6 L/hour (range 2.2 to 6.1).

(100 mg)

A multiple-dose, steady-state study was conducted in sixteen normal subjects, with three 100 mg tablets given every 12 hours for eight doses. Three high fat content meals were served at 6:30 a.m.,12 noon and 6:30 p.m. Dosing began one-half hour after the evening meal with the test dose occurring one-half hour after breakfast. At steady-state following the eighth dose, the mean Cmax was 8.1 mcg/mL and the mean Cmin was 5.6 mcg/mL. The mean time to peak concentration was 6.2 hours. The average percent fraction of fluctuation was 45%.

The subjects used for this study were the same as those used in the previously cited 200 mg study.

Once-a-Day Dosing

A multiple-dose, steady-state study was conducted under fed conditions with once-a-day dosing. Fed conditions were the same as those previously cited. Sixteen subjects were dosed at 2 x 300 mg tablets every morning at 8 a.m. for five doses. At steady-state, the mean Cmax was 11.7 mcg/mL, and the mean Cmin was 3.4 mcg/mL. The average percent fraction of fluctuation was 244%. The mean Tmax was 8.7 hours.

The subjects used in the above study exhibited a mean half-life of 7.9 hours (range 5.3 to 13.4) and a mean clearance of 3.8 L/hour (range 2.3 to 5.7).

Distribution

Once theophylline enters the systemic circulation, about 40% is bound to plasma protein, primarily albumin. Unbound theophylline distributes throughout body water, but distributes poorly into body fat. The apparent volume of distribution of theophylline is approximately 0.45 L/kg (range 0.3 to 0.7 L/kg) based on ideal body weight. Theophylline passes freely across the placenta, into breast milk and into the cerebrospinal fluid (CSF). Saliva theophylline concentrations approximate unbound serum concentrations, but are not reliable for routine or therapeutic monitoring unless special techniques are used. An increase in the volume of distribution of theophylline, primarily due to reduction in plasma protein binding, occurs in premature neonates, patients with hepatic cirrhosis, uncorrected acidemia, the elderly and in women during the third trimester of pregnancy. In such cases, the patient may show signs of toxicity at total (bound + unbound) serum concentrations of theophylline in the therapeutic range (10 to 20 mcg/mL) due to elevated concentrations of the pharmacologically active unbound drug. Similarly, a patient with decreased theophylline binding may have a sub-therapeutic total drug concentration while the pharmacologically active unbound concentration is in the therapeutic range. If only total serum theophylline concentration is measured, this may lead to an unnecessary and potentially dangerous dose increase. In patients with reduced protein binding, measurement of unbound serum theophylline concentration provides a more reliable means of dosage adjustment than measurement of total serum theophylline concentration. Generally, concentrations of unbound theophylline should be maintained in the range of 6 to 12 mcg/mL.

Metabolism

Following oral dosing, theophylline does not undergo any measurable first-pass elimination. In adults and children beyond one year of age, approximately 90% of the dose is metabolized in the liver. Biotransformation takes place through demethylation to 1-methylxanthine and 3-methylxanthine and hydroxylation to 1,3-dimethyluric acid. 1-methylxanthine is further hydroxylated, by xanthine oxidase, to 1-methyluric acid. About 6% of a theophylline dose is N-methylated to caffeine. Theophylline demethylation to 3-methylxanthine is catalyzed by cytochrome P-450 1A2, while cytochromes P-450 2E1 and P-450 3A3 catalyze the hydroxylation to 1,3-dimethyluric acid. Demethylation to 1-methyl-xanthine appears to be catalyzed either by cytochrome P-450 1A2 or a closely related cytochrome. In neonates, the N-demethylation pathway is absent while the function of the hydroxylation pathway is markedly deficient. The activity of these pathways slowly increases to maximal levels by one year of age.

Caffeine and 3-methylxanthine are the only theophylline metabolites with pharmacologic activity. 3-methylxanthine has approximately one tenth the pharmacologic activity of theophylline and serum concentrations in adults with normal renal function are less than 1 mcg/mL. In patients with end-stage renal disease, 3-methylxanthine may accumulate to concentrations that approximate the unmetabolized theophylline concentration. Caffeine concentrations are usually undetectable in adults regardless of renal function. In neonates, caffeine may accumulate to concentrations that approximate the unmetabolized theophylline concentration and thus, exert a pharmacologic effect.

Both the N-demethylation and hydroxylation pathways of theophylline biotransformation are capacity-limited. Due to the wide intersubject variability of the rate of theophylline metabolism, non-linearity of elimination may begin in some patients at serum theophylline concentrations greater than 10 mcg/mL. Since this non-linearity results in more than proportional changes in serum theophylline concentrations with changes in dose, it is advisable to make increases or decreases in dose in small increments in order to achieve desired changes in serum theophylline concentrations (see DOSAGE AND ADMINISTRATION, Table VI). Accurate prediction of dose-dependency of theophylline metabolism in patients a priori is not possible, but patients with very high initial clearance rates (i.e., low steady-state serum theophylline concentrations at above average doses) have the greatest likelihood of experiencing large changes in serum theophylline concentration in response to dosage changes.

Excretion

In neonates, approximately 50% of the theophylline dose is excreted unchanged in the urine. Beyond the first three months of life, approximately 10% of the theophylline dose is excreted unchanged in the urine. The remainder is excreted in the urine mainly as 1,3-dimethyluric acid (35 to 40%), 1-methyluric acid (20 to 25%) and 3-methylxanthine (15 to 20%). Since little theophylline is excreted unchanged in the urine and since active metabolites of theophylline (i.e., caffeine, 3-methylxanthine) do not accumulate to clinically significant levels even in the face of end-stage renal disease, no dosage adjustment for renal insufficiency is necessary in adults and children greater than 3 months of age. In contrast, the large fraction of the theophylline dose excreted in the urine as unchanged theophylline and caffeine in neonates requires careful attention to dose reduction and frequent monitoring of serum theophylline concentrations in neonates with reduced renal function (see WARNINGS).

Serum Concentrations at Steady-State

After multiple doses of theophylline, steady-state is reached in 30 to 65 hours (average 40 hours) in adults. At steady-state, on a dosage regimen with 6-hour intervals, the expected mean trough concentration is approximately 60% of the mean peak concentration, assuming a mean theophylline half-life of 8 hours. The difference between peak and trough concentrations is larger in patients with more rapid theophylline clearance. In patients with high theophylline clearance and half-lives of about 4 to 5 hours, such as children age 1 to 9 years, the trough serum theophylline concentration may be only 30% of peak with a 6-hour dosing interval. In these patients a slow-release formulation would allow a longer dosing interval (8 to 12 hours) with a smaller peak/trough difference.

Special Populations (see Table I for mean clearance and half-life values)

Geriatric

The clearance of theophylline is decreased by an average of 30% in healthy elderly adults (greater than 60 yrs) compared to healthy young adults. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in elderly patients (see WARNINGS).

Pediatrics

The clearance of theophylline is very low in neonates (see WARNINGS). Theophylline clearance reaches maximal values by one year of age, remains relatively constant until about 9 years of age and then slowly decreases by approximately 50% to adult values at about age 16. Renal excretion of unchanged theophylline in neonates amounts to about 50% of the dose, compared to about 10% in children older than three months and in adults. Careful attention to dosage selection and monitoring of serum theophylline concentrations are required in pediatric patients (see WARNINGS and DOSAGE AND ADMINISTRATION).

Gender

Gender differences in theophylline clearance are relatively small and unlikely to be of clinical significance. Significant reduction in theophylline clearance, however, has been reported in women on the 20th day of the menstrual cycle and during the third trimester of pregnancy.

Race

Pharmacokinetic differences in theophylline clearance due to race have not been studied.

Renal Insufficiency

Only a small fraction, e.g., about 10%, of the administered theophylline dose is excreted unchanged in the urine of children greater than three months of age and adults. Since little theophylline is excreted unchanged in the urine and since active metabolites of theophylline (i.e., caffeine, 3-methylxanthine) do not accumulate to clinically significant levels even in the face of end-stage renal disease, no dosage adjustment for renal insufficiency is necessary in adults and children greater than 3 months of age. In contrast, approximately 50% of the administered theophylline dose is excreted unchanged in the urine in neonates. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in neonates with decreased renal function (see WARNINGS).

Hepatic Insufficiency

Theophylline clearance is decreased by 50% or more in patients with hepatic insufficiency (e.g., cirrhosis, acute hepatitis, cholestasis). Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in patients with reduced hepatic function (see WARNINGS).

Congestive Heart Failure (CHF)

Theophylline clearance is decreased by 50% or more in patients with CHF. The extent of reduction in theophylline clearance in patients with CHF appears to be directly correlated to the severity of the cardiac disease. Since theophylline clearance is independent of liver blood flow, the reduction in clearance appears to be due to impaired hepatocyte function rather than reduced perfusion. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in patients with CHF (see WARNINGS).

Smokers

Tobacco and marijuana smoking appears to increase the clearance of theophylline by induction of metabolic pathways. Theophylline clearance has been shown to increase by approximately 50% in young adult tobacco smokers and by approximately 80% in elderly tobacco smokers compared to nonsmoking subjects. Passive smoke exposure has also been shown to increase theophylline clearance by up to 50%. Abstinence from tobacco smoking for one week causes a reduction of approximately 40% in theophylline clearance. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in patients who stop smoking (see WARNINGS). Use of nicotine gum has been shown to have no effect on theophylline clearance.

Fever

Fever, regardless of its underlying cause, can decrease the clearance of theophylline. The magnitude and duration of the fever appear to be directly correlated to the degree of decrease of theophylline clearance. Precise data are lacking, but a temperature of 39°C (102°F) for at least 24 hours is probably required to produce a clinically significant increase in serum theophylline concentrations. Children with rapid rates of theophylline clearance (i.e., those who require a dose that is substantially larger than average [e.g., greater than 22 mg/kg/day] to achieve a therapeutic peak serum theophylline concentration when afebrile) may be at greater risk of toxic effects from decreased clearance during sustained fever. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in patients with sustained fever (see WARNINGS).

Miscellaneous

Other factors associated with decreased theophylline clearance include the third trimester of

pregnancy, sepsis with multiple organ failure, and hypothyroidism. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in patients with any of these conditions (see WARNINGS). Other factors associated with increased theophylline clearance include hyperthyroidism and cystic fibrosis.

Clinical Studies

In patients with chronic asthma, including patients with severe asthma requiring inhaled corticosteroids or alternate-day oral corticosteroids, many clinical studies have shown that theophylline decreases the frequency and severity of symptoms, including nocturnal exacerbations, and decreases the “as needed” use of inhaled beta-2 agonists. Theophylline has also been shown to reduce the need for short courses of daily oral prednisone to relieve exacerbations of airway obstruction that are unresponsive to bronchodilators in asthmatics.

In patients with chronic obstructive pulmonary disease (COPD), clinical studies have shown that theophylline decreases dyspnea, air trapping, the work of breathing, and improves contractility of diaphragmatic muscles with little or no improvement in pulmonary function measurements.

INDICATIONS AND USAGE

Theophylline extended-release tablets are indicated for the treatment of the symptoms and reversible airflow obstruction associated with chronic asthma and other chronic lung diseases, e.g., emphysema and chronic bronchitis.

CONTRAINDICATIONS

Theophylline extended-release tablets are contraindicated in patients with a history of hypersensitivity to theophylline or other components in the product.

WARNINGS

Concurrent Illness

Theophylline should be used with extreme caution in patients with the following clinical conditions due to the increased risk of exacerbation of the concurrent condition:

Active peptic ulcer disease

Seizure disorders

Cardiac arrhythmias (not including bradyarrhythmias).

Conditions that Reduce Theophylline Clearance

There are several readily identifiable causes of reduced theophylline clearance.If the total daily dose is not appropriately reduced in the presence of these risk factors, severe and potentially fatal theophylline toxicity can occur. Careful consideration must be given to the benefits and risks of theophylline use and the need for more intensive monitoring of serum theophylline concentrations in patients with the following risk factors:

Age

Neonates (term and premature), children less than 1 year, elderly (greter than 60 years).

Concurrent Diseases

Acute pulmonary edema, congestive heart failure, cor-pulmonale, fever (greater than or equal to 102° for 24 hours or more; or lesser temperature elevations for longer periods), reduced renal function in infants less than 3 months of age, sepsis with multi-organ failure, and shock.

Cessation of Smoking

Drug Interactions

Adding a drug that inhibits theophylline metabolism (e.g., cimetidine, erythromycin, tacrine) or stopping a concurrently administered drug that enhances theophylline metabolism (e.g., carbamazepine, rifampin). (see PRECAUTIONS, Drug Interactions, Table II).

When Signs or Symptoms of Theophylline Toxicity Are Present

Whenever a patient receiving theophylline develops nausea or vomiting, particularly repetitive vomiting, or other signs or symptoms consistent with theophylline toxicity (even if another cause may be suspected), additional doses of theophylline should be withheld and a serum theophylline concentration measured immediately. Patients should be instructed not to continue any dosage that causes adverse effects and to withhold subsequent doses until the symptoms have resolved, at which time the clinician may instruct the patient to resume the drug at a lower dosage (see DOSAGE AND ADMINISTRATION, Dosing Guidelines,Table VI).

Dosage Increases

Increases in the dose of theophylline should not be made in response to an acute exacerbation of symptoms of chronic lung disease since theophylline provides little added benefit to inhaled beta2-selective agonists and systemically administered cortico-steroids in this circumstance and increases the risk of adverse effects. A peak steady-state serum theophylline concentration should be measured before increasing the dose in response to persistent chronic symptoms to ascertain whether an increase in dose is safe. Before increasing the theophylline dose on the basis of a low serum concentration, the clinician should consider whether the blood sample was obtained at an appropriate time in relationship to the dose and whether the patient has adhered to the prescribed regimen (see PRECAUTIONS, Laboratory Tests).

As the rate of theophylline clearance may be dose-dependent (i.e., steady-state serum concentrations may increase disproportionately to the increase in dose), an increase in dose based upon a sub-therapeutic serum concentration measurement should be conservative. In general, limiting dose increases to about 25% of the previous total daily dose will reduce the risk of unintended excessive increases in serum theophylline concentration (see DOSAGE AND ADMINISTRATION, Table VI).

PRECAUTIONS

General

Careful consideration of the various interacting drugs and physiologic conditions that can alter theophylline clearance and require dosage adjustment should occur prior to initiation of theophylline therapy, prior to increases in theophylline dose, and during follow up (see WARNINGS). The dose of theophylline selected for initiation of therapy should be low and, if tolerated, increased slowly over a period of a week or longer with the final dose guided by monitoring serum theophylline concentrations and the patient’s clinical response (see DOSAGE AND ADMINISTRATION, Table V).

Monitoring Serum Theophylline Concentrations

Serum theophylline concentration measurements are readily available and should be used to determine whether the dosage is appropriate. Specifically, the serum theophylline concentration should be measured as follows:

1. When initiating therapy to guide final dosage adjustment after titration.
2. Before making a dose increase to determine whether the serum concentration is subtherapeutic in a patient who continues to be symptomatic.
3. Whenever signs or symptoms of theophylline toxicity are present.
4. Whenever there is a new illness, worsening of a chronic illness or a change in the patient's treatment regimen that may alter theophylline clearance (e.g., fever greater than 102°F sustained for greater than or equal to 24 hours, hepatitis, or drugs listed in Table II are added or discontinued).

To guide a dose increase, the blood sample should be obtained at the time of the expected peak serum theophylline concentration: 6 to 7 hours after a dose at steady-state. For most patients, steady-state will be reached after 3 days of dosing when no doses have been missed, no extra doses have been added, and none of the doses have been taken at unequal intervals. A trough concentration (i.e., at the end of the dosing interval) provides no additional useful information and may lead to an inappropriate dose increase since the peak serum theophylline concentration can be two or more times greater than the trough concentration with an immediate-release formulation. If the serum sample is drawn more than seven hours after the dose, the results must be interpreted with caution since the concentration may not be reflective of the peak concentration. In contrast, when signs or symptoms of theophylline toxicity are present, the serum sample should be obtained as soon as possible, analyzed immediately, and the result reported to the clinician without delay. In patients in whom decreased serum protein binding is suspected (e.g., cirrhosis, women during the third trimester of pregnancy), the concentration of unbound theophylline should be measured and the dosage adjusted to achieve an unbound concentration of 6 to 12 mcg/mL.

Saliva concentrations of theophylline cannot be used reliably to adjust dosage without special techniques.

Effects on Laboratory Tests

As a result of its pharmacological effects, theophylline at serum concentrations within the 10 to 20 mcg/mL range modestly increases plasma glucose (from a mean of 88 mg% to 98 mg%), uric acid (from a mean of 4 mg/dL to 6 mg/dL), free fatty acids (from a mean of 451 µεq/L to 800 µεq/L, total cholesterol (from a mean of 140 vs 160 mg/dL), HDL (from a mean of 36 to 50 mg/dL), HDL/LDL ratio (from a mean of 0.5 to 0.7), and urinary free cortisol excretion (from a mean of 44 to 63 mcg/24 hr). Theophylline at serum concentrations within the 10 to 20 mcg/mL range may also transiently decrease serum concentrations of triiodothyronine (144 before, 131 after one week and 142 ng/dl after 4 weeks of theophylline). The clinical importance of these changes should be weighed against the potential therapeutic benefit of theophylline in individual patients.

Information for Patients

The patient (or parent/care giver) should be instructed to seek medical advice whenever nausea, vomiting, persistent headache, insomnia or rapid heart beat occurs during treatment with theophylline, even if another cause is suspected. The patient should be instructed to contact their clinician if they develop a new illness, especially if accompanied by a persistent fever, if they experience worsening of a chronic illness, if they start or stop smoking cigarettes or marijuana, or if another clinician adds a new medication or discontinues a previously prescribed medication. Patients should be instructed to inform all clinicians involved in their care that they are taking theophylline, especially when a medication is

being added or deleted from their treatment. Patients should be instructed to not alter the dose, timing of the dose, or frequency of administration without first consulting their clinician. If a dose is missed, the patient should be instructed to take the next dose at the usually scheduled time and to not attempt to make up for the missed dose.

Theophylline extended-release tablets should not be chewed or crushed. When dosing on a once daily (q24h) basis, tablets should be taken whole and not split.

Drug Interactions

Drug-Drug Interactions

Theophylline interacts with a wide variety of drugs. The interaction may be pharmacodynamic, i.e., alterations in the therapeutic response to theophylline or another drug or occurrence of adverse effects without a change in serum theophylline concentration. More frequently, however, the interaction is pharmacokinetic, i.e., the rate of theophylline clearance is altered by another drug resulting in increased or decreased serum theophylline concentrations. Theophylline only rarely alters the pharmacokinetics of other drugs.

The drugs listed in Table II have the potential to produce clinically significant pharmacodynamic or pharmacokinetic interactions with theophylline. The information in the “Effect” column of Table II assumes that the interacting drug is being added to a steady-state theophylline regimen. If theophylline is being initiated in a patient who is already taking a drug that inhibits theophylline clearance (e.g., cimetidine, erythromycin), the dose of theophylline required to achieve a therapeutic serum theophylline concentration will be smaller. Conversely, if theophylline is being initiated in a patient who is already taking a drug that enhances theophylline clearance (e.g., rifampin), the dose of theophylline required to achieve a therapeutic serum theophylline concentration will be larger. Discontinuation of a concomitant drug that increases theophylline clearance will result in accumulation of theophylline to potentially toxic levels, unless the theophylline dose is appropriately reduced. Discontinuation of a concomitant drug that inhibits theophylline clearance will result in decreased serum theophylline concentrations, unless the theophylline dose is appropriately increased.

The drugs listed in Table III have either been documented not to interact with theophylline or do not produce a clinically significant interaction (i.e., greater than 15% change in theophylline clearance).

The listing of drugs in Tables II and III are current as of February 9, 1995. New interactions are continuously being reported for theophylline, especially with new chemical entities. The clinician should not assume that a drug does not interact with theophylline if it is not listed in Table II. Before addition of a newly available drug in a patient receiving theophylline, the package insert of the new drug and/or the medical literature should be consulted to determine if an interaction between the new drug and theophylline has been reported.

Table II. Clinically significant drug interactions with theophylline.*

Drug	Type of Interaction	Effect†
Adenosine	Theophylline blocks adenosine receptors.	Higher doses of adenosine may berequired to achieve desired effect.
Alcohol	A single large dose of alcohol (3 mL/kg ofwhiskey) decreases theophylline clearance for up to24 hours	30% increase
Allopurinol	Decreases theophylline clearance at	25% increase

Allopurinol	allopurinoldoses 600 mg/day	25% increase
Aminoglutethimide	Increases theophylline clearance by induction ofmicrosomal enzyme activity.	25% decrease
Carbamazepine	Similar to aminoglutethimide.	30% decrease
Cimetidine	Decreases theophylline clearance by inhibitingcytochrome P450 1A2	70% increase
Ciprofloxacin	Similar to cimetidine.	40% increase
Clarithromycin	Similar to erythromycin.	25% increase
Diazepam	Benzodiazepines increase CNS concentratrionsof adenosine, a potent CNS depressant, whiletheophylline blocks adenosine receptors.	Larger diazepam doses may be requiredto produce desired level of sedation.Discontinuation of theophylline withoutreduction of diazepam dose may resultin respiratory depression.
Disulfiram	Decreases theophylline clearance by inhibitinghydroxylation and demethylation.	50% increase
Enoxacin	Similar to cimetidine.	300% increase
Ephedrine	Synergistic CNS effects	Increased frequency of nausea,nervousness, and insomnia.
Erythromycin	Erythromycin metabolite decreases theophyllineclearance by inhibiting cytochrome P450 3A3.	35% increase. Erythromycin steady-state serum concentrations decrease by asimilar amount.
Estrogen	Estrogen containing oral contraceptives decreasetheophylline clearance in a dose-dependentfashion. The effect of progesterone on theophyllineclearance in unknown.	30% increase
Flurazepam	Similar to diazepam.	Similar to diazepam.
Fluvoxamine	Similar to cimetidine.	Similar to cimetidine.
Halothane	Halothane sensitizes the myocardium tocatecholamines, theophylline increases release ofendogenous catecholamines.	Increased risk of ventriculararrhythmias.
Interferon, human recombinant alpha-A	Decreases theophylline clearance.	100% increase
Isoproterenol (IV)	Increase theophylline clearance.	20% increase
Ketamine	Pharmacologic	May lower theophylline seizurethreshold.
Lithium	Theophylline increases renal lithium clearance.	Lithium dose required to achievea therapeutic serum concentrationincreased an average of 60%.
Lorazepam	Similar to diazepam.	Similar to diazepam.
Methotrexate (MTX)	Decreases theophylline clearance.	20% increase after low dose MTX,higher dose MTX may have a greatereffect.
Mexiletine	Similar to disulfiram.	80% increase
Midazolam	Similar to diazepam.	Similar to diazepam.

Moricizine	Increases theophylline clearance.	25% increase
Pancuronium	Theophylline may antagonize non-depolarizingneuromuscular blocking effects;possibly due tophosphodiesterase inhibition.	Larger dose of pancuronium may berequired to achieve neuromuscularblockade.
Pentoxifylline	Decreases theophylline clearance.	30% increase
Phenobarbital (PB)	Similar to aminoglutethimide.	25% decrease after two weeks ofconcurrent PB.
Phenytoin	Phenytoin increases theophylline clearance byincreasing microsomal enzyme activity.	Serum theophylline and phenytoinconcentrations decrease about 40%.
Propafenone	Decreases theophylline clearance andpharmacologic interaction.	40% increase. Beta-2 blocking effectmay decrease efficacy of theophylline.
Propranolol	Similar to cimetidine and pharmacologicinteraction.	100% increase Beta-2 blocking effectmay decrease efficacy of theophylline
Rifampin	Increases theophylline clearance by increasingcytochrome P450 1A2 and 3A3 activity.	20-40% decrease
Sulfinpyrazone	Increase theophylline clearance by increasingdemethylation and hydroxylation. Decreases renalclearance of theophylline.	20% increase
Tacrine	Similar to cimetidine, also increases renalclearance of theophylline.	90% increase
Thiabendazole	Decreases theophylline clearance.	190% increase
Ticlopidine	Decreases theophylline clearance.	60% increase
Troleandomycin	Similar to erythromycin.	33-100% increase depending ontroleandomycin dose.
Verapamil	Similar to disulfiram.	20% increase

* Refer to PRECAUTIONS, Drug Interactions for further information regarding table.
† Average effect on steady-state theophylline concentration or other clinical effect for pharmacologic interactions. Individual patients may experience larger changes in serum theophylline concentration than the value listed.

Table III. Drugs that have been documented not to interact with theophylline or drugs that produce no clinically significant interaction with theophylline.*

albuterol,	famotidine	nizatidine
systemic and inhaled	felodipine	norfloxacin
amoxicillin	finasteride	ofloxacin
ampicillin,	hydrocortisone	omeprazole
with or without	isoflurane	prednisone, prednisolone
sulbactam	isoniazid	ranitidine
atenolol	isradipine	rifabutin

azithromycin	influenza vaccine	roxithromycin
caffeine,	ketoconazole	sorbitol
dietary digestion	lomefloxacin	(purgative doses do not
cefaclor	mebendazole	inhibit theophylline
co-trimoxazole	medroxyprogesterone	absorption)
(trimethoprim and	methylprednisolone	sucralfate
sulfamethoxazole)	metronidazole	terbutaline, systemic
diltiazem	metoprolol	terfenadine
dirithromycin	nadolol	tetracycline
enflurane	nifedipine	tocainide

* Refer to PRECAUTIONS, Drug Interactions for information regarding table.

Drug-Food Interactions

Taking theophylline extended-release tablets immediately after ingesting a high fat content meal (45 g fat, 55 g carbohydrates, 28 g protein, 789 calories) may result in a somewhat higher Cmax and delayed Tmax, and a somewhat greater extent of absorption when compared to taking it in the fasting state. The influence of the type and amount of other foods, as well as the time interval between drug and food, has not been studied.

The Effect of Other Drugs on Theophylline Serum Concentration Measurements
Most serum theophylline assays in clinical use are immunoassays which are specific for theophylline. Other xanthines such as caffeine, dyphylline, and pentoxifylline are not detected by these assays. Some drugs (e.g., cefazolin, cephalothin), however, may interfere with certain HPLC techniques. Caffeine and xanthine metabolites in neonates or patients with renal dysfunction may cause the reading from some dry reagent office methods to be higher than the actual serum theophylline concentration.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term carcinogenicity studies have been carried out in mice (oral doses 30 to 150 mg/kg) and rats (oral doses 5 to 75 mg/kg). Results are pending.

Theophylline has been studied in Ames salmonella, in vivo and in vitro cytogenetics, micronucleus and Chinese hamster ovary test systems and has not been shown to be genotoxic.

In a 14 week continuous breeding study, theophylline, administered to mating pairs of B6C3F1 mice at oral doses of 120, 270 and 500 mg/kg (approximately 1.0 to 3.0 times the human dose on a mg/m2 basis) impaired fertility, as evidenced by decreases in the number of live pups per litter, decreases in the mean number of litters per fertile pair, and increases in the gestation period at the high dose as well as decreases in the proportion of pups born alive at the mid and high dose. In 13 week toxicity studies, theophylline was administered to F344 rats and B6C3F1 mice at oral doses of 40 to 300 mg/kg (approximately 2.0 times the human dose on a mg/m2 basis). At the high dose, systemic toxicity was observed in both species including decreases in testicular weight.

Pregnancy

Category C

There are no adequate and well-controlled studies in pregnant women. Additionally, there are no teratogenicity studies in non-rodents (e.g., rabbits). Theophylline was not shown to be teratogenic in CD-1 mice at oral doses up to 400 mg/kg, approximately 2.0 times the human dose on a mg/m2 basis or

in CD-1 rats at oral doses up to 260 mg/kg, approximately 3.0 times the recommended human dose on a mg/m2 basis. At a dose of 220 mg/kg, embryotoxicity was observed in rats in the absence of maternal toxicity.

Nursing Mothers

Theophylline is excreted into breast milk and may cause irritability or other signs of mild toxicity in nursing human infants. The concentration of theophylline in breast milk is about equivalent to the maternal serum concentration. An infant ingesting a liter of breast milk containing 10 to 20 mcg/mL of theophylline a day is likely to receive 10 to 20 mg of theophylline per day. Serious adverse effects in the infant are unlikely unless the mother has toxic serum theophylline concentrations.

Pediatric Use

Theophylline is safe and effective for the approved indications in pediatric patients. The maintenance dose of theophylline must be selected with caution in pediatric patients since the rate of theophylline clearance is highly variable across the age range of neonates to adolescents (see CLINICAL PHARMACOLOGY, Table I, WARNINGS, and DOSAGE AND ADMINISTRATION, Table V).

Geriatric Use

Elderly patients are at significantly greater risk of experiencing serious toxicity from theophylline than younger patients due to pharmacokinetic and pharmacodynamic changes associated with aging. Theophylline clearance is reduced in patients greater than 60 years of age, resulting in increased serum theophylline concentrations in response to a given theophylline dose. Protein binding may be decreased in the elderly resulting in a larger proportion of the total serum theophylline concentration in the pharmacologically active unbound form. Elderly patients also appear to be more sensitive to the toxic effects of theophylline after chronic overdosage than younger patients. For these reasons, the maximum daily dose of theophylline in patients greater than 60 years of age ordinarily should not exceed 400 mg/day unless the patient continues to be symptomatic and the peak steady-state serum theophylline concentration is less than 10 mcg/mL (see DOSAGE AND ADMINISTRATION). Theophylline doses greater than 400 mg/d should be prescribed with caution in elderly patients.

ADVERSE REACTIONS

Adverse reactions associated with theophylline are generally mild when peak serum theophylline concentrations are less than 20 mcg/mL and mainly consist of transient caffeine-like adverse effects such as nausea, vomiting, headache, and insomnia. When peak serum theophylline concentrations exceed 20 mcg/mL, however, theophylline produces a wide range of adverse reactions including persistent vomiting, cardiac arrhythmias, and intractable seizures which can be lethal (see OVERDOSAGE). The transient caffeine-like adverse reactions occur in about 50% of patients when theophylline therapy is initiated at doses higher than recommended initial doses (e.g., greater than 300 mg/day in adults and greater than 12 mg/kg/day in children beyond 1 year of age). During the initiation of theophylline therapy, caffeine-like adverse effects may transiently alter patient behavior, especially in school age children, but this response rarely persists. Initiation of theophylline therapy at a low dose with subsequent slow titration to a predetermined age-related maximum dose will significantly reduce the frequency of these transient adverse effects (see DOSAGE AND ADMINISTRATION, Table V). In a small percentage of patients (less than 3% of children and less than 10% of adults) the caffeine-like adverse effects persist during maintenance therapy, even at peak serum theophylline concentrations within the therapeutic range (i.e., 10 to 20 mcg/mL). Dosage reduction may alleviate the caffeine-like adverse effects in these patients, however, persistent adverse effects should result in a reevaluation of the need for continued theophylline therapy and the potential therapeutic benefit of alternative treatment.

Other adverse reactions that have been reported at serum theophylline concentrations less than 20 mcg/mL include diarrhea, irritability, restlessness, fine skeletal muscle tremors, and transient diuresis.

In patients with hypoxia secondary to COPD, multifocal atrial tachycardia and flutter have been reported at serum theophylline concentrations greater than or equal to 15 mcg/mL. There have been a few isolated reports of seizures at serum theophylline concentrations less than 20 mcg/mL in patients with an underlying neurological disease or in elderly patients. The occurrence of seizures in elderly patients with serum theophylline concentrations less than 20 mcg/mL may be secondary to decreased protein binding resulting in a larger proportion of the total serum theophylline concentration in the pharmacologically active unbound form. The clinical characteristics of the seizures reported in patients with serum theophylline concentrations less than 20 mcg/mL have generally been milder than seizures associated with excessive serum theophylline concentrations resulting from an overdose (i.e., they have generally been transient, often stopped without anticonvulsant therapy, and did not result in neurological residua).

Table IV. Manifestations of theophylline toxicity.* Percentage of patients reported with sign or symptom

	Acute Overdose (Large Single Ingestion)		Chronic Overdosage (Multiple Excessive Doses)	
Sign/Symptom	Study 1	Study 2	Study 1	Study 2
Asymotomatic	(n= 157)	(n= 14)	(n=92)	(n=102)
Gastointestinal	NR†	0	NR†	6
Vomiting	73	93	30	61
Abdominal Pain	NR†	21	NR†	12
Diarrhea	NR†	0	NR†	14
Hematemesis	NR†	0	NR†	2
Metabolic/Other				
Hypokalemia	85	79	44	43
Hyperglycemia	98	NR†	18	NR†
Acid/base disturbance	34	21	9	5
Rhabdomyolysis	NR†	7	NR†	0
Cardiovascular				
Sinus tachycardia	100	86	100	62
Other supraventricular tachycardias	2	21	12	14
Ventricular premature beats	3	21	10	19
Atrial fibrillation or flutter	1	NR†	12	NR†
Multifocal atrial tachycardia	0	NR†	2	NR†
Ventricular arrhythmias	7	14	40	0
hemodynamic instability				
Hypotension/shock	NR†	21	NR†	8
Neurologic				
Nervousness	NR†	64	NR†	21
Tremors	38	29	16	14
Disorientation	NR†	7	NR†	11
Seizures	5	14	14	5
Death	3	21	10	4

* These data are derived from two studies in patients with serum theophylline concentrations greater than 30 mcg/mL. In the first study (Study #1 - Shanon, Ann Intern Med 1993;119:1161-67), data were prospectively collected from 249 consecutive cases of theophylline toxicity referred to a regional poison center for consultation. In the second study (Study #2 - Sessler, Am J Med 1990;88:567-76), data were retrospectively collected from 116 cases with serum theophylline concentrations greater than 30

mcg/mL among 6000 blood samples obtained for measurement of serum theophylline concentrations in three emergency departments. Differences in the incidence of manifestations of theophylline toxicity between the two studies may reflect sample selection as a result of study design (e.g., in Study #1, 48% of the patients had acute intoxications versus only 10% in Study #2) and different methods of reporting results.

† NR = Not reported in a comparable manner.

OVERDOSAGE

General

The chronicity and pattern of theophylline overdosage significantly influences clinical manifestations of toxicity, management and outcome. There are two common presentations: (1) acute overdose, i.e., ingestion of a single large excessive dose (greater than 10 mg/kg) as occurs in the context of an attempted suicide or isolated medication error, and (2) chronic overdosage, i.e., ingestion of repeated doses that are excessive for the patient's rate of theophylline clearance. The most common causes of chronic theophylline overdosage include patient or care giver error in dosing, clinician prescribing of an excessive dose or a normal dose in the presence of factors known to decrease the rate of theophylline clearance, and increasing the dose in response to an exacerbation of symptoms without first measuring the serum theophylline concentration to determine whether a dose increase is safe.

Severe toxicity from theophylline overdose is a relatively rare event. In one health maintenance organization, the frequency of hospital admissions for chronic overdosage of theophylline was about 1 per 1000 person-years exposure. In another study, among 6000 blood samples obtained for measurement of serum theophylline concentration, for any reason, from patients treated in an emergency department, 7% were in the 20 to 30 mcg/mL range and 3% were greater than 30 mcg/mL. Approximately two-thirds of the patients with serum theophylline concentrations in the 20 to 30 mcg/mL range had one or more manifestations of toxicity while greater than 90% of patients with serum theophylline concentrations greater than 30 mcg/mL were clinically intoxicated. Similarly, in other reports, serious toxicity from theophylline is seen principally at serum concentrations greater than 30 mcg/mL.

Several studies have described the clinical manifestations of theophylline overdose and attempted to determine the factors that predict life-threatening toxicity. In general, patients who experience an acute overdose are less likely to experience seizures than patients who have experienced a chronic overdosage, unless the peak serum theophylline concentration is greater than 100 mcg/mL. After a chronic overdosage, generalized seizures, life-threatening cardiac arrhythmias, and death may occur at serum theophylline concentrations greater than 30 mcg/mL. The severity of toxicity after chronic overdosage is more strongly correlated with the patient's age than the peak serum theophylline concentration; patients greater than 60 years are at the greatest risk for severe toxicity and mortality after a chronic overdosage. Preexisting or concurrent disease may also significantly increase the susceptibility of a patient to a particular toxic manifestation, e.g., patients with neurologic disorders have an increased risk of seizures and patients with cardiac disease have an increased risk of cardiac arrhythmias for a given serum theophylline concentration compared to patients without the underlying disease.

The frequency of various reported manifestations of theophylline overdose according to the mode of overdose are listed in Table IV.

Other manifestations of theophylline toxicity include increases in serum calcium, creatine kinase, myoglobin and leukocyte count, decreases in serum phosphate and magnesium, acute myocardial infarction, and urinary retention in men with obstructive uropathy.

Seizures associated with serum theophylline concentrations greater than 30 mcg/mL are often resistant to anticonvulsant therapy and may result in irreversible brain injury if not rapidly controlled. Death from theophylline toxicity is most often secondary to cardiorespiratory arrest and/or hypoxic encephalopathy following prolonged generalized seizures or intractable cardiac arrhythmias causing hemodynamic compromise.

Overdose Management

General Recommendations for Patients with Symptoms of Theophylline Overdose or Serum Theophylline Concentrations greater than 30 mcg/mL (Note: Serum theophylline concentrations may continue to increase after presentation of the patient for medical care.)

1. While simultaneously instituting treatment, contact a regional poison center to obtain updated information and advice on individualizing the recommendations that follow.
2. Institute supportive care, including establishment of intravenous access, maintenance of the airway, and electrocardiographic monitoring.
3. Treatment of seizures : Because of the high morbidity and mortality associated with theophylline-induced seizures, treatment should be rapid and aggressive. Anticonvulsant therapy should be initiated with an intravenous benzodiazepine, e.g., diazepam, in increments of 0.1 to 0.2 mg/kg every 1 to 3 minutes until seizures are terminated. Repetitive seizures should be treated with a loading dose of phenobarbital (20 mg/kg infused over 30 to 60 minutes). Case reports of theophylline overdose in humans and animal studies suggest that phenytoin is ineffective in terminating theophylline-induced seizures. The doses of benzodiazepines and phenobarbital required to terminate theophylline-induced seizures are close to the doses that may cause severe respiratory depression or respiratory arrest; the clinician should therefore be prepared to provide assisted ventilation. Elderly patients and patients with COPD may be more susceptible to the respiratory depressant effects of anticonvulsants. Barbiturate-induced coma or administration of general anesthesia may be required to terminate repetitive seizures or status epilepticus. General anesthesia should be used with caution in patients with theophylline overdose because fluorinated volatile anesthetics may sensitize the myocardium to endogenous catecholamines released by theophylline. Enflurane appears less likely to be associated with this effect than halothane and may, therefore, be safer. Neuromuscular blocking agents alone should not be used to terminate seizures since they abolish the musculoskeletal manifestations without terminating seizure activity in the brain.
4. Anticipate need for anticonvulsants: In patients with theophylline overdose who are at high risk for theophylline-induced seizures, e.g., patients with acute overdoses and serum theophylline concentrations greater than 100 mcg/mL or chronic overdosage in patients greater than 60 years of age with serum theophylline concentrations greater than 30 mcg/mL, the need for anticonvulsant therapy should be anticipated. A benzodiazepine such as diazepam should be drawn into a syringe and kept at the patient’s bedside and medical personnel qualified to treat seizures should be immediately available. In selected patients at high risk for theophylline-induced seizures, consideration should be given to the administration of prophylactic anticonvulsant therapy. Situations where prophylactic anticonvulsant therapy should be considered in high risk patients include anticipated delays in instituting methods for extracorporeal removal of theophylline (e.g., transfer of a high risk patient from one health care facility to another for extracorporeal removal) and clinical circumstances that significantly interfere with efforts to enhance theophylline clearance (e.g., a neonate where dialysis may not be technically feasible or a patient with vomiting unresponsive to antiemetics who is unable to tolerate multiple-dose oral activated charcoal). In animal studies, prophylactic administration of phenobarbital, but not phenytoin, has been shown to delay the onset of theophylline-induced generalized seizures and to increase the dose of theophylline required to induce seizures (i.e., markedly increases the LD50). Although there are no controlled studies in humans, a loading dose of intravenous phenobarbital (20 mg/kg infused over 60 minutes) may delay or prevent life-threatening seizures in high risk patients while efforts to enhance theophylline clearance are continued. Phenobarbital may cause respiratory depression, particularly in

elderly patients and patients with COPD.
5. Treatment of cardiac arrhythmias: Sinus tachycardia and simple ventricular premature beats are not harbingers of life-threatening arrhythmias, they do not require treatment in the absence of hemodynamic compromise, and they resolve with declining serum theophylline concentrations. Other arrhythmias, especially those associated with hemodynamic compromise, should be treated with antiarrhythmic therapy appropriate for the type of arrhythmia.
6. Gastrointestinal decontamination : Oral activated charcoal (0.5 g/kg up to 20 g and repeat at least once 1 to 2 hours after the first dose) is extremely effective in blocking the absorption of theophylline throughout the gastrointestinal tract, even when administered several hours after ingestion. If the patient is vomiting, the charcoal should be administered through a nasogastric tube or after administration of an antiemetic. Phenothiazine antiemetics such as prochlorperazine or perphenazine should be avoided since they can lower the seizure threshold and frequently cause dystonic reactions. A single dose of sorbitol may be used to promote stooling to facilitate removal of theophylline bound to charcoal from the gastrointestinal tract. Sorbitol, however, should be dosed with caution since it is a potent purgative which can cause profound fluid and electrolyte abnormalities, particularly after multiple doses. Commercially available fixed combinations of liquid charcoal and sorbitol should be avoided in young children and after the first dose in adolescents and adults since they do not allow for individualization of charcoal and sorbitol dosing. Ipecac syrup should be avoided in theophylline overdoses. Although ipecac induces emesis, it does not reduce the absorption of theophylline unless administered within 5 minutes of ingestion and even then is less effective than oral activated charcoal. Moreover, ipecac induced emesis may persist for several hours after a single dose and significantly decrease the retention and the effectiveness of oral activated charcoal.
7. Serum theophylline concentration monitoring: The serum theophylline concentration should be measured immediately upon presentation, 2 to 4 hours later, and then at sufficient intervals, e.g., every 4 hours, to guide treatment decisions and to assess the effectiveness of therapy. Serum theophylline concentrations may continue to increase after presentation of the patient for medical care as a result of continued absorption of theophylline from the gastrointestinal tract. Serial monitoring of serum theophylline serum concentrations should be continued until it is clear that the concentration is no longer rising and has returned to nontoxic levels.
8. General monitoring procedures: Electrocardiographic monitoring should be initiated on presentation and continued until the serum theophylline level has returned to a nontoxic level. Serum electrolytes and glucose should be measured on presentation and at appropriate intervals indicated by clinical circumstances. Fluid and electrolyte abnormalities should be promptly corrected. Monitoring and treatment should be continued until the serum concentration decreases below 20 mcg/mL.
9. Enhance clearance of theophylline: Multiple-dose oral activated charcoal (e.g., 0.5 mg/kg up to 20 g, every two hours) increases the clearance of theophylline at least twofold by absorption of theophylline secreted into gastrointestinal fluids. Charcoal must be retained in, and pass through, the gastrointestinal tract to be effective; emesis should therefore be controlled by administration of appropriate antiemetics. Alternatively, the charcoal can be administered continuously through a nasogastric tube in conjunction with appropriate antiemetics. A single dose of sorbitol may be administered with the activated charcoal to promote stooling to facilitate clearance of the adsorbed theophylline from the gastrointestinal tract. Sorbitol alone does not enhance clearance of theophylline and should be dosed with caution to prevent excessive stooling which can result in severe fluid and electrolyte imbalances. Commercially available fixed combinations of liquid charcoal and sorbitol should be avoided in young children and after the first dose in adolescents and adults since they do not allow for individualization of charcoal and sorbitol dosing. In patients with intractable vomiting, extracorporeal methods of theophylline removal should be instituted (see OVERDOSAGE, Extracorporeal Removal).

Specific Recommendations

Acute Overdose

A. Serum Concentration greater than 20 less than 30 mcg/mL

1. Administer a single dose of oral activated charcoal.

2. Monitor the patient and obtain a serum theophylline concentration in 2 to 4 hours to insure that the concentration is not increasing.

B. Serum Concentration greater than 30 less than 100 mcg/mL

1. Administer multiple-dose oral activated charcoal and measures to control emesis.

2. Monitor the patient and obtain serial theophylline concentrations every 2 to 4 hours to gauge the effectiveness of therapy and to guide further treatment decisions.

3. Institute extracorporeal removal if emesis, seizures, or cardiac arrhythmias cannot be adequately controlled (see OVERDOSAGE, Extracorporeal Removal).

C. Serum Concentration greater than 100 mcg/mL

1. Consider prophylactic anticonvulsant therapy.

2. Administer multiple-dose oral activated charcoal and measures to control emesis.

3. Consider extracorporeal removal, even if the patient has not experienced a seizure (see OVERDOSAGE, Extracorporeal Removal).

4. Monitor the patient and obtain serial theophylline concentrations every 2 to 4 hours to gauge the effectiveness of therapy and to guide further treatment decisions.

Chronic Overdosage

A. Serum Concentration greater than 20 less than 30 mcg/mL (with manifestations of theophylline toxicity)

1. Administer a single dose of oral activated charcoal.

2. Monitor the patient and obtain a serum theophylline concentration in 2 to 4 hours to insure that the concentration is not increasing.

B. Serum Concentration greater than 30 mcg/mL in patients less than 60 years of age

1. Administer multiple-dose oral activated charcoal and measures to control emesis.

2. Monitor the patient and obtain serial theophylline concentrations every 2 to 4 hours to gauge the effectiveness of therapy and to guide further treatment decisions.

3. Institute extracorporeal removal if emesis, seizures, or cardiac arrhythmias cannot be

adequately controlled (see OVERDOSAGE, Extracorporeal Removal).

C. Serum Concentration greater than 30 mcg/mL in patients greater than 60 years of age

1. Consider prophylactic anticonvulsant therapy.

2. Administer multiple-dose oral activated charcoal and measures to control emesis.

3. Consider extracorporeal removal even if the patient has not experienced a seizure (see

OVERDOSAGE, Extracorporeal Removal).

4. Monitor the patient and obtain serial theophylline concentrations every 2 to 4 hours to gauge

the effectiveness of therapy and to guide further treatment decisions.

Extracorporeal Removal

Increasing the rate of theophylline clearance by extracorporeal methods may rapidly decrease serum concentrations, but the risks of the procedure must be weighed against the potential benefit. Charcoal hemoperfusion is the most effective method of extracorporeal removal, increasing theophylline clearance up to sixfold, but serious complications, including hypotension, hypocalcemia, platelet consumption and bleeding diatheses may occur. Hemodialysis is about as efficient as multiple-dose oral activated charcoal and has a lower risk of serious complications than charcoal hemoperfusion. Hemodialysis should be considered as an alternative when charcoal hemoperfusion is not feasible and multiple-dose oral charcoal is ineffective because of intractable emesis. Serum theophylline concentrations may rebound 5 to 10 mcg/mL after discontinuation of charcoal hemoperfusion or hemodialysis due to redistribution of theophylline from the tissue compartment. Peritoneal dialysis is ineffective for theophylline removal; exchange transfusions in neonates have been minimally effective.

DOSAGE AND ADMINISTRATION

Taking theophylline extended-release tablets immediately after a high-fat content meal may result in a somewhat higher Cmax and delayed Tmax, and somewhat greater extent of absorption. However, the differences are usually not great and this product may normally be administered without regard to meals (see CLINICAL PHARMACOLOGY, Drug Interactions, Drug-Food Interactions).

Theophylline extended-release tablets are recommended for chronic or long-term management and prevention of symptoms, and not for use in treating acute symptoms of asthma and reversible bronchospasm.

General Considerations

The steady-state peak serum theophylline concentration is a function of the dose, the dosing interval, and the rate of theophylline absorption and clearance in the individual patient. Because of marked individual differences in the rate of theophylline clearance, the dose required to achieve a peak serum theophylline concentration in the 10 to 20 mcg/mL range varies fourfold among otherwise similar patients in the absence of factors known to alter theophylline clearance (e.g., 400 to 1600 mg/day in adults less than 60 years old and 10 to 36 mg/kg/day in children 1 to 9 years old). For a given population there is no single theophylline dose that will provide both safe and effective serum concentrations for all patients. Administration of the median theophylline dose required to achieve a therapeutic serum theophylline concentration in a given population may result in either subtherapeutic or potentially toxic

serum theophylline concentrations in individual patients. For example, at a dose of 900 mg/d in adults less than 60 years or 22 mg/kg/d in children 1 to 9 years, the steady-state peak serum theophylline concentration will be less than 10 mcg/mL in about 30% of patients, 10 to 20 mcg/mL in about 50% and 20 to 30 mcg/mL in about 20% of patients. The dose of theophylline must be individualized on the basis of peak serum theophylline concentration measurements in order to achieve a dose that will provide maximum potential benefit with minimal risk of adverse effects.

Transient caffeine-like adverse effects and excessive serum concentrations in slow metabolizers can be avoided in most patients by starting with a sufficiently low dose and slowly increasing the dose, if judged to be clinically indicated, in small increments (see Table V). Dose increases should only be made if the previous dosage is well tolerated and at intervals of no less than 3 days to allow serum theophylline concentrations to reach the new steady state. Dosage adjustment should be guided by serum theophylline concentration measurement (see PRECAUTIONS, Laboratory Tests and DOSAGE AND ADMINISTRATION, Table VI). Health care providers should instruct patients and care givers to discontinue any dosage that causes adverse effects, to withhold the medication until these symptoms are gone and to then resume therapy at a lower, previously tolerated dosage (see WARNINGS).

If the patient's symptoms are well controlled, there are no apparent adverse effects, and no intervening factors that might alter dosage requirements (see WARNINGS and PRECAUTIONS), serum theophylline concentrations should be monitored at 6 month intervals for rapidly growing children and at yearly intervals for all others. In acutely ill patients, serum theophylline concentrations should be monitored at frequent intervals, e.g. every 24 hours.

Theophylline distributes poorly into body fat, therefore, mg/kg dose should be calculated on the basis of ideal body weight.

Table V contains theophylline dosing titration schema recommended for patients in various age groups and clinical circumstances. Table VI contains recommendations for theophylline dosage adjustment based upon serum theophylline concentrations. Application of these general dosing recommendations to individual patients must take into account the unique clinical characteristics of each patient. In general, these recommendations should serve as the upper limit for dosage adjustments in order to decrease the risk of potentially serious adverse events associated with unexpected large increases in serum theophylline concentration.

A. Children (6-15 years) and adults (16-60 years) without risk factors for impaired clearance.

Table V. Dosing initiation and titration (as anhydrous theophylline).*

Titration Step 1. Starting Dosage	Children less than 45 kg 12-14 mg/kg/day up to a maximum of 300 mg/day divided Q12 hrs*	Children >45 kg and adults 300 mg/day divided Q12 hrs*
2. After 3 days, if tolerated. increase dose to:	16 mf/kg/day up to a maximum of 400 mg/day divided Q12 hrs*	400 mg/day divided Q12 hrs*
3. After 3 more days, if tolerated. increase dose to:	20 mg/kg/day up to a maximum of 600 mg/day divided Q12 hrs*	600 mg/day divided Q12 hrs*

B. Patients With Risk Factors For Impaired Clearance, The Elderly (greater than 60 Years), And Those In Whom It Is Not Feasible To Monitor Serum Theophylline Concentrations:
In children 6-15 years of age, the final theophylline dose should not exceed 16 mg/kg/day up to a maximum of 400 mg/day in the
presence of risk factors for reduced theophylline clearance (see WARNINGS) or if it is not feasible to monitor serum theophylline
concentrations.
In adolescents ³16 years and adults, including the elderly, the final theophylline dose should not exceed 400 mg/day in the presence of
risk factors for reduced theophylline clearance (see WARNINGS) or if it is not feasible to monitor serum theophylline concentrations.

*Patients with more rapid metabolism, clinically identified by higher than average dose requirements, should receive a smaller dose
more frequently (every 8 hours) to prevent breakthrough symptoms resulting from low trough concentrations before the next dose

Table VI. Dosage adjustment guided by serum theophylline concentration.

Peak Serum Concentration	Dosage Adjustment
less than 9.9 mcg/mL	If symptoms are not controlled and current dosage is tolerated, increase dose about 25%. Recheck serum concentration after three days for further dosage adjustment.
10 to 14.9 mcg/mL	If symptoms are controlled and current dosage is tolerated, maintain dose and recheck serum concentration at 6-12 month intervals.* If symptoms are not controlled and current dosage is tolerated consider adding additional medication(s) to treatment regimen.
15-19.9 mcg/mL	Consider 10% decrease in dose to provide greater margin of safety even if current dosage is tolerated.*
	Decrease dose by 25% even if no adverse

20-24.9 mcg/mL	effects are present. Recheck serum concentration after 3 days to guide further dosage adjustment.
25-30 mcg/mL	Skip next dose and decrease subsequent doses at least 25% even if no adverse effects are present. Recheck serum concentration after 3 days to guide further dosage adjustment. If symptomatic, consider whether overdose treatment is indicated (see recommendations for chronic overdosage).
greater than 30 mcg/mL	Treat overdose as indicated (see recommendations for chronic overdosage). If theophylline is subsequently resumed, decrease dose by at least 50% and recheck serum concentration after 3 days to guide further dosage adjustment.
* Dose reduction and/or serum theophylline concentration measurement is indicated whenever adverse effects are present, physiologic abnormalities that can reduce theophylline clearance occur (e.g., sustained fever), or a drug that interacts with theophylline is added or discontinued (see WARNINGS).	

Once-Daily Dosing

The slow absorption rate of this preparation may allow once-daily administration in adult non-smokers with appropriate total body clearance and other patients with low dosage requirements. Once-daily dosing should be considered only after the patient has been gradually and satisfactorily titrated to therapeutic levels with q12h dosing. Once-daily dosing should be based on twice the q12h dose and should be initiated at the end of the last q12h dosing interval. The trough concentration (Cmin) obtained following conversion to once-daily dosing may be lower (especially in high clearance patients) and the peak concentration (Cmax) may be higher (especially in low clearance patients) than that obtained with q12h dosing. If symptoms recur, or signs of toxicity appear during the once-daily dosing interval, dosing on the q12h basis should be reinstituted.

It is essential that serum theophylline concentrations be monitored before and after transfer to once-daily dosing.

Food and posture, along with changes associated with circadian rhythm, may influence the rate of absorption and/or clearance rates of theophylline from extended-release dosage forms administered at night. The exact relationship of these and other factors to nighttime serum concentrations and the clinical significance of such findings require additional study. Therefore, it is not recommended that theophylline extended-release once-daily dosing be administered at night.

HOW SUPPLIED

Theophylline Extended-Release Tablets

100 mg – White to off white, round, biconvex, uncoated tablets debossed with PLIVA and 483 bisected by a score line on one side and unscored on the other side in bottles of 100 and 500.

200 mg – White to off white, Oval shaped, biconvex, uncoated tablets debossed with PLIVA and 482 on one side and scored on the other side in bottles of 100, 500 and 1000.

300 mg – White to off white, capsule shaped, biconvex, uncoated tablets debossed with PLIVA and 459 on one side and scored on the other side in bottles of 100, 500 and 1000.

450 mg – White to off white, capsule shaped, biconvex, uncoated tablets debossed with PLIVA and 518 on one side and scored on the other side in bottles of 100.

Manufactured In India By:
EMCURE PHARMACEUTICALS LTD.
Hinjwadi, Pune, India

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev. A 6/2010

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

NDC 50111-483-01 THEOPHYLLINE EXTENDED-RELEASE Tablets 100 mg Rx only
100 TABLETS TEVA Each extended-release tablet contains 100 mg theophylline (anhydrous), USP. Usual Dosage: See package insert for full prescribing information. Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. Manufactured In India By: EMCURE PHARMACEUTICALS LTD. Hinjwadi, Pune, India.411057 Manufactured For: TEVA PHARMACEUTICALS USA Sellersville, PA 18960 50111-483-01 Iss. 7/2009 10001954

Sentra AM™ PRODUCT INFORMATION Sentra AM (U.S. patent pending) capsules by oral administration. A specially formulated Medical Food product, consisting of a proprietary blend of amino acids and polyphenol ingredients in specific proportions, for the nutritional management of the metabolic processes of fatigue and cognitive disorders (FCD). Must be administered under physician

supervision. Medical Foods Medical Food products are often used in hospitals (e.g., for burn victims or kidney dialysis patients) and outside of a hospital setting under a physician's care for the nutritional management of diseases in patients with particular medical or metabolic needs due to their disease or condition. Congress defined "Medical Food" in the Orphan Drug Act and Amendments of 1988 as "a food which is formulated to be consumed or administered enterally [or orally] under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." Medical Foods are complex formulated products, requiring sophisticated and exacting technology. Sentra AM has been developed, manufactured, and labeled in accordance with both the statutory and the FDA regulatory definition of a Medical Food. Sentra AM must be used while the patient is under the ongoing care of a physician. FATIGUE AND COGNITIVE DISORDERS (FCD) FCD as a Metabolic Deficiency Disease A critical component of the definition of a Medical Food is the requirement for a distinctive nutritional deficiency. FDA scientists have proposed a physiologic definition of a distinctive nutritional deficiency as follows: "the dietary management of patients with specific diseases requires, in some instances, the ability to meet nutritional requirements that differ substantially from the needs of healthy persons. For example, in establishing the recommended dietary allowances for general, healthy population, the Food and Nutrition Board of the Institute of Medicine National Academy of Sciences, recognized that different or distinctive physiologic requirements may exist for certain persons with "special nutritional needs arising from metabolic disorders, chronic diseases, injuries, premature birth, other medical conditions and drug therapies. Thus, the distinctive nutritional needs associated with a disease reflect the total amount needed by a healthy person to support life or maintain homeostasis, adjusted for the distinctive changes in the nutritional needs of the patient as a result of the effects of the disease process on absorption, metabolism, and excretion." It was also proposed that in patients with certain disease states who respond to nutritional therapies, a physiologic deficiency of the nutrient is assumed to exist. For example, if a patient with fatigue and cognitive disorders responds to a choline formulation by decreasing perceived fatigue and increasing cognitive function, a deficiency of choline is assumed to exist. Patients with fatigue and cognitive disorders are known to have nutritional deficiencies of choline, flavonoids, and certain antioxidants. Patients with fatigue and cognitive disorders frequently exhibit reduced plasma levels of choline and have been shown to respond to oral administration of a choline formulation. Research has shown that choline reduced diets result in a fall of circulating choline. Patients with fatigue and cognitive disorders sometimes have activation of the degradation pathways that increase the turnover of choline leading to a reduced level of production of acetylcholine for a given choline blood level. Research has also shown that a genetic predisposition to accelerated degradation of choline can lead to increased precursor requirements in certain patients with fatigue and cognitive disorders. Choline is required to fully potentiate acetylcholine synthesis by brain neurons. A deficiency of choline leads to reduced acetylcholine production by the neurons. Patients with fatigue and cognitive disorders frequently consume diets that are choline deficient. Flavonoids potentiate the production of acetylcholine by the neurons thereby reducing fatigue and cognitive impairment. Diets deficient in flavonoid rich foods result in inadequate flavonoid concentrations, impeding acetylcholine production in certain patients with fatigue and cognitive disorders. Acetylcholine in pre-synaptic and post-synaptic ganglia is necessary for neuronal function. Provision of choline and flavonoids with antioxidants, in specific proportions can restore the production of beneficial acetylcholine, thereby reducing fatigue and improving cognitive function.

PRODUCT DESCRIPTION Primary Ingredients Sentra AM consists of a proprietary blend of amino acids, cocoa, and flavonoids in specific proportions. These ingredients fall into the category of "Generally Regarded as Safe" (GRAS) as defined by the Food and Drug Administration (FDA) (Sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act). A GRAS substance is distinguished from a food additive on the basis of the common knowledge about the safety of the substance for its intended use. The standard for an ingredient to achieve GRAS status requires not only technical demonstration of non-toxicity and safety, but also general recognition of safety through widespread usage and agreement of that safety by experts in the field. Many ingredients have been

determined by the U.S. Food and Drug Administration (FDA) to be GRAS, and are listed as such by regulation, in Volume 21 Code of Federal Regulations (CFR) Sections 182, 184, and 186. Amino Acids Amino Acids are the building blocks of protein. All amino acids are GRAS listed as they have been ingested by humans for thousands of years. The doses of the amino acids, particularly choline, in Sentra AM are equivalent to those found in the usual human diet; however the formulation uses specific ratios of the key ingredients to elicit a therapeutic response. Patients with fatigue and cognitive disorders may require an increased amount of certain amino acids that cannot be obtained from normal diet alone. Choline, for example, is an obligatory amino acid. The body cannot make choline and must obtain choline from the diet. Choline is needed to produce acetylcholine. Acetylcholine is required to reduce fatigue and improve cognitive function. Patients with fatigue and cognitive disorders have altered choline metabolism. Some patients with fatigue and cognitive disorders have a resistance to the metabolism of choline that is similar to the mechanism found in insulin resistance. Patients with fatigue and cognitive disorders cannot acquire sufficient choline from the diet without ingesting a prohibitively large amount of calories, particularly calories from protein. Flavonoids Flavonoids are a group of phytochemical compounds found in all vascular plants including fruits and vegetables. They are a part of a larger class of compounds known as polyphenols. Many of the therapeutic or health benefits of colored fruits and vegetables, cocoa, red wine, and green tea are directly related to their flavonoid content. The specially formulated flavonoids found in Sentra AM cannot be obtained from conventional foods in the necessary proportions to elicit a therapeutic response. Physical Description Sentra AM is a yellow to light brown powder. Sentra AM contains L-Glutamic Acid, Choline Bitartrate, Cocoa, Acetylcarnitine, and Hawthorn Berry. Other Ingredients Sentra AM contains the following inactive or other ingredients as fillers, excipients, and colorings: magnesium stearate, microcrystalline cellulose, Maltodextrin NF, gelatin (as the capsule material).

CLINICAL PHARMACOLOGY Mechanism of Action Sentra AM acts by restoring and maintaining the balance of the neurotransmitter acetylcholine that is associated with fatigue and cognitive disorders. Metabolism The amino acids in Sentra AM are primarily absorbed by the stomach and small intestines. All cells metabolize the amino acids in Sentra AM. Circulating choline blood levels determine the production of acetylcholine. Excretion Sentra AM is not an inhibitor of cytochrome P450 1A2, 2C9, 2C19, 2D6, or 3A4.These isoenzymes are principally responsible for 95% of all detoxification of drugs, with CYP3A4 being responsible for detoxification of roughly 50% of drugs. Amino acids do not appear to have an effect on drug metabolizing enzymes. Sentra AM does not directly interact with prescription drugs. Pharmaceutical administration may allow for lowering of the drug dose under physician supervision.

INDICATIONS FOR USE Sentra AM is intended for the clinical nutritional management of the metabolic processes associated with fatigue and cognitive disorders. - Chronic fatigue - Cognitive impairment - Fibromyalgia

CLINICAL EXPERIENCE Administrations of Sentra AM has demonstrated significant functional improvements when used for the nutritional management of the metabolic processes associated with fatigue and cognitive disorders. Administration of Sentra AM results in the reduction of fatigue and cognitive impairment. Sentra AM has no effect on normal blood pressure.

PRECAUTIONS AND CONTRAINDICATIONS Sentra AM is contraindicated in an extremely small number of patients with hypersensitivity to any of the nutritional components of Sentra AM.

ADVERSE REACTIONS Oral administration of choline at high doses up to 15 grams daily is generally well tolerated. The most common adverse reactions of higher doses — from 15 to 30 grams daily — are nausea, abdominal cramps, and diarrhea. Some patients may experience these symptoms at lower doses. The total combined amount of amino acids in each Sentra AM capsule does not exceed 400 mg.

DRUG INTERACTIONS Sentra AM does not directly influence the pharmacokinetics of prescription drugs. Clinical experience has shown that administration of Sentra AM may allow for lowering the dose of co-administered drugs under physician supervision.

OVERDOSE There is a negligible risk of overdose with Sentra AM as the total dosage of amino acids in a one month supply (60 capsules) is less than 25 grams. Overdose symptoms may include diarrhea, weakness, and nausea. POST-MARKETING SURVEILLANCE Post-marketing surveillance has shown no significant adverse reactions. Reported cases of mild rash and itching may have been associated with allergies to Sentra AM flavonoid ingredients, including cinnamon, cocoa, and chocolate. The reactions were transient in nature and subsided within 24 hours.

DOSAGE AND ADMINISTRATION Recommended Administration For the nutritional management of the metabolic processes in patients with fatigue and cognitive disorders. Take (2) capsules one to three times daily or as directed by physician. As with most amino acid formulations Sentra AM should be taken between meals without food to increase the absorption of key ingredients.

How Supplied Sentra AM is supplied in opaque orange and white, size 0 capsules in bottles of 60 capsules. Physician Supervision Sentra AM is a Medical Food product available by prescription only and must be used while the patient is under ongoing physician supervision. U.S. patent pending. Manufactured by Arizona Nutritional Supplements, Inc. Chandler AZ 85225 Distributed by Physician Therapeutics LLC, Los Angeles, CA 90077. www.ptlcentral.com NDC # 68405-1002-02

Storage Store at room temperature, 59-86OF (15-30OC) Protect from light and moisture. Sentra AM is supplied to physicians in a recyclable plastic bottle with a child-resistant cap.

PHYSICIAN THERAPEUTICS SENTRA AM Medical Food Rx only 60 Capsules Directions for use: Must be administered under medical supervision. For adults only. As a Medical Food, take two (2) capsules in the morning on an empty stomach or as directed by your medical practitioner. For the dietary management of chronic fatigue syndromes. Contains no added sugar, starch, wheat, yeast, preservatives, artificial color or flavor. Storage: Keep tightly closed in a cool dry place 8-320 C (45-900F), relative humidity, below 50%. Warning: Keep this product out of the reach of children. NDC# 68405-1002-02 Ingredients: Each serving (2 capsules) contains: Proprietary Amino Acid Blend Choline Bitartrate, L-Glutamic Acid, Cocoa Extract (fruit), Acetyl L-Carnitine HCI Proprietary Herbal Blend Ginkgo Biloba (leaves), Hawthorn Berry (fruit), Dextrose Other Ingredients: Gelatin, Cellulose, Dicalcium Phosphate, Silicon Dioxide and Vegetable Magnesium Stearate. Distributed by: Physician Therapeutics LLC, Los Angeles, CA 90077 www.ptlcentral.com Patent Pending

For the Dietary Management of Cognitive Disorders. Two capsules in the morning or as directed by physician. See product label and insert. Sentra AM Medical Food A Convenience Pakced Medical Food and Drug Senophylline PHYSICIAN THERAPEUTICS > Sentra AM 60 Capsules > Theophylline 100 mg 30 Tablets Rx Only No Refills Without Physician Authorization NDC # 68405-8002-06 of this co-pack FRONT VIEW As prescribed by physician. See product label and product information insert. Theophylline 100 mg Rx Drug 68405-8002-06 BACK VIEW

52959-0341-30

CAUTION: Federal law PROHIBITS the transfer of this drug to anyone other than the person to whom prescribed and prohibits dispensing without a prescription unless OTC. See outsert for add'l RX info KEEP OUT O REACH OF CHILDREN. Store in a cool dry place at 68 to 77 degrees F.

THEOPHYLLINE C.R. 100mg TABLET

Lot #: TL01B #30

Mfg: BARR

Exp: 08/12

Compare to: Theo-Dur

Mfg. NDC: 50111-0483-02

Take as directed by your Doctor or
See outsert for usual dosage information

THEOPHYLLINE C.R. 100mg TABLET
52959-0341-30 Qty #30
08/12 Lot TL01B
Theo-Dur 50111-0483-02

THEOPHYLLINE C.R. 100mg TABLET
52959-0341-30 Qty #30
08/12 Lot TL01B
Theo-Dur 50111-0483-02

THEOPHYLLINE C.R. 100mg TABLET
52959-0341-30 Qty #30
08/12 Lot TL01B
Theo-Dur 50111-0483-02

THEOPHYLLINE C.R. 100mg TABLET
52959-0341-30 Qty #30
08/12 Lot TL01B
Theo-Dur 50111-0483-02

Repack: HJ Harkins Co., Inc. Nipomo, CA 93444

SENOPHYLLINE

theophylline anhydrous, choline kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68405-002

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68405-002-06	1 in 1 KIT		

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	2 BOTTLE	60
Part 2	1 BOTTLE	60

Part 1 of 2

THEOPHYLLINE

theophylline anhydrous capsule

Product Information	
Item Code (Source)	NDC:52959-341(NDC:50111-483)
Route of Administration	ORAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
THEOPHYLLINE ANHYDROUS (UNII: 0I55128JYK) (THEOPHYLLINE ANHYDROUS - UNII:0I55128JYK)	THEOPHYLLINE ANHYDROUS	100 mg

Inactive Ingredients	
Ingredient Name	**Strength**
HYPROMELLOSE 2208 (100 MPA.S) (UNII: B1QE5P712K)	
HYPROMELLOSE 2208 (100000 MPA.S) (UNII: VM7F0B23ZI)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POVIDONE K30 (UNII: U725QWY32X)	

Product Characteristics			
Color	white (white to off white)	**Score**	2 pieces
Shape	ROUND	**Size**	10mm
Flavor		**Imprint Code**	PLIVA;483
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:52959-341-30	30 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA089807	07/07/2011	

Part 2 of 2

SENTRA AM

choline capsule

Product Information

Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CHOLINE (UNII: N91BDP6H0X) (CHOLINE - UNII:N91BDP6H0X)	CHOLINE	250 mg

Inactive Ingredients

Ingredient Name	Strength
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
MALTODEXTRIN (UNII: 7CVR7L4A2D)	
GELATIN (UNII: 2G86QN327L)	

Product Characteristics

Color	orange (ORANGE)	**Score**	no score
Shape	CAPSULE	**Size**	21mm
Flavor		**Imprint Code**	;
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		60 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
Medical Food		07/07/2011	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date

unapproved drug other		07/07/2011	

Labeler - Physician Therapeutics LLC (931940964)

Establishment

Name	Address	ID/FEI	Business Operations
Emcure Pharmaceuticals Ltd.		916921919	manufacture

Establishment

Name	Address	ID/FEI	Business Operations
H.J. Harkins Company, Inc.		147681894	repack

Establishment

Name	Address	ID/FEI	Business Operations
Targeted Medical Pharma, Inc.		126962740	manufacture

Revised: 8/2011 Physician Therapeutics LLC