

## Theophylline (Anhydrous) Extended-Release Tablets 400 mg and 600 mg Rx only

### DESCRIPTION

Theophylline (Anhydrous) Extended-Release Tablets in a controlled-release system allows a 24-hour dosing interval for appropriate patients.

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:



The molecular formula of anhydrous theophylline is C<sub>7</sub>H<sub>8</sub>N<sub>4</sub>O<sub>2</sub> with a molecular weight of 180.17. Each Extended-Release tablet for oral administration, contains 400 or 600 mg of anhydrous theophylline per tablet.

Inactive ingredients: glyceryl behenate, silicified microcrystalline cellulose, silicon dioxide, and magnesium stearate.

### 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 II 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 III or antagonism of adenosine receptors. Some of the adverse effects associated with theophylline appear to be mediated by inhibition of PDE III (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 5-20 mcg/mL. Clinically important improvement in symptom control has been found in most studies to require peak serum theophylline concentrations >10 mcg/mL, but patients with mild disease may benefit from lower concentrations. At serum theophylline concentrations >20mcg/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-hour intervals) and periodically in patients receiving long-term therapy, e.g., at 6-12 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                                 | Total body clearance* Mean (range)†† (mL/kg/min) | Half-life mean (range)†† (hr) |
|--|--|-------------------------------|
| <b>Age</b>   |  |                               |
| Premature neonates   |  |                               |
| postnatal age 3-15 days                                    | 0.29 (0.09-0.49)                                 | 30 (17-43)                    |
| postnatal age 25-57 days                                   | 0.64 (0.04-1.2)                                  | 20 (9.4-30.6)                 |
| Term infants   |  |                               |
| postnatal age 1-2 days                                     | NR†  | 25.7 (25-26.5)                |
| postnatal age 3-20 weeks                                   | NR†  | 11 (6-29)                     |
| Children   |  |                               |
| 1-4 years  | 1.7 (0.5-2.9)                                    | 3.4 (1.2-5.6)                 |
| 4-12 years   | 1.6 (0.8-2.4)                                    | NR†                           |
| 13-15 years  | 0.9 (0.48-1.3)                                   | NR†                           |
| 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)                  |
| <b>Concurrent illness or altered physiological state</b>   |  |                               |
| 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 (10-13)                   |
| 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 (8.4-17.8)               |
| 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)                 |

†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 <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

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

**Absorption** Theophylline (Anhydrous) Extended-Release Tablets administered in the fed state is completely absorbed after oral administration.

In a single-dose crossover study, two 400 mg Theophylline (Anhydrous) Extended-Release Tablets were administered to 19 normal volunteers in the morning or evening immediately following the same standardized meal (769 calories consisting of 97 grams carbohydrates, 33 grams protein and 27 grams fat). There was no evidence of dose dumping nor were there any significant differences in pharmacokinetic parameters attributable to time of drug administration. On the morning arm, the pharmacokinetic parameters were AUC=241.9 ± 63.0 mcg hr/mL, Cmax=9.3 ± 2.0 mcg/mL, Tmax=12.8 ± 4.2 hours. On the evening arm, the pharmacokinetic parameters were AUC=219.7 ± 83.0 mcg hr/mL, Cmax=9.2 ± 2.0 mcg/mL, Tmax=12.5 ± 4.2 hours.

A study in which Theophylline (Anhydrous) Extended-Release 400 mg Tablets were administered to 17 fed adult asthmatics produced similar theophylline level-time curves when administered in the morning or evening. Serum levels were generally higher in the evening regimen but there were no statistically significant differences between the two regimens.

|                            | MORNING      | EVENING      |
|----------------------------|--------------|--------------|
| AUC (0-24 hrs) (mcg hr/mL) | 236.0 ± 76.7 | 256.0 ± 80.4 |
| Cmax (mcg/mL)              | 14.5 ± 4.1   | 16.3 ± 4.4   |
| Cmin (mcg/mL)              | 5.5 ± 2.9    | 5.0 ± 2.5    |
| Tmax (hours)               | 8.1 ± 3.7    | 10.1 ± 4.1   |

A single-dose study in 15 normal fasting male volunteers whose theophylline inherent mean elimination half-life was verified by a liquid theophylline product to be 6.9 ± 2.5 (S.D.) hours were administered two or three 400 mg Theophylline (Anhydrous) Extended-Release Tablets. The relative bioavailability of Theophylline (Anhydrous) Extended-Release Tablets given in the fasting state in comparison to an immediate-release product was 59%. Peak serum theophylline levels occurred at 6.9 ± 5.2 (S.D.) hours, with a normalized (to 800 mg) peak level being 6.2 ± 2.1 (S.D.). The apparent elimination half-life for the 400 mg Theophylline (Anhydrous) Extended-Release Tablets was 17.2 ± 5.8 (S.D.) hours. Steady-state pharmacokinetics were determined in a study in 12 fasted patients with chronic reversible obstructive pulmonary disease. All were dosed with two 400 mg Theophylline (Anhydrous) Extended-

Release Tablets given once daily in the morning and a reference controlled-release BID product administered as two 200 mg tablets given 12 hours apart. The pharmacokinetic parameters obtained for Theophylline (Anhydrous) Extended-Release Tablets given at doses of 800 mg once daily in the morning were virtually identical to the corresponding parameters for the reference drug when given as 400 mg BID. In particular, the AUC, Cmax and Cmin values obtained in this study were as follows:

|                              | Theophylline (Anhydrous) Extended-Release Tablets 800 mg Q 24 h ± S.D. | Reference Drug 400 mg Q12h ± S.D. |
|------------------------------|--|-----------------------------------|
| AUC, (0-24 hours), mcg hr/mL | 288.9 ± 21.5   | 283.5 ± 38.4                      |
| Cmax, mcg/mL                 | 15.7 ± 2.8   | 15.2 ± 2.1                        |
| Cmin, mcg/mL                 | 7.9 ± 1.6  | 7.8 ± 1.7                         |
| Cmax-Cmin diff.              | 7.7 ± 1.5  | 7.4 ± 1.5                         |

Single-dose studies in which subjects were fasted for twelve (12) hours prior to and an additional four (4) hours following dosing, demonstrated reduced bioavailability as compared to dosing with food. One single-dose study in 20 normal volunteers dosed with two (2) 400 mg tablets in the morning, compared dosing during these fasting conditions with dosing immediately prior to a standardized breakfast (769 calories, consisting of 97 grams carbohydrates, 33 grams protein and 27 grams fat). Under fasted conditions, the pharmacokinetic parameters were AUC=231.7 ± 92.4 mcg hr/mL, Cmax=8.4 ± 2.6 mcg/mL, Tmax=17.3 ± 6.7 hours. Under fasting conditions, these parameters were AUC=141.2 ± 6.53 mcg hr/mL, Cmax=5.5 ± 1.5 mcg/mL, Tmax=6.5 ± 2.1 hours.

Another single-dose study in 21 normal male volunteers, dosed in the evening, compared fasting to a standardized high calorie, high fat meal (870-1,020 calories, consisting of 33 grams protein, 55-75 grams fat, 58 grams carbohydrates). In the fasting arm subjects received one Theophylline (Anhydrous) Extended-Release 400 mg Tablet at 8 p.m. after an eight hour fast followed by a further four hour fast. In the fed arm, subjects were again dosed with one 400 mg Theophylline (Anhydrous) Extended-Release Tablet, but at 8 p.m. immediately after the high fat content standardized meal cited above. The pharmacokinetic parameters (normalized to 800 mg) fed were AUC=221.8 ± 40.9 mcg hr/mL, Cmax=10.9 ± 1.7 mcg/mL, Tmax=11.8 ± 2.2 hours. In the fasting arm, the pharmacokinetic parameters (normalized to 800 mg) were AUC=146.4 ± 40.9 mcg hr/mL, Cmax= 6.7 ± 1.7 mcg/mL, Tmax=7.2 ± 2.2 hours.

Thus, administration of single Theophylline (Anhydrous) Extended-Release doses to healthy normal volunteers, under prolonged fasted conditions (at least 10 hour overnight fast before dosing followed by an additional four (4) hour fast after dosing) results in decreased bioavailability. However, there was no failure of this delivery system leading to a sudden and unexpected release of a large quantity of theophylline with Theophylline (Anhydrous) Extended-Release Tablets even when they are administered with a high fat, high calorie meal.

Similar studies were conducted with the 600 mg Theophylline (Anhydrous) Extended-Release Tablet. A single-dose study in 24 subjects with an established theophylline clearance of ≤ 4 L/hr, compared the pharmacokinetic evaluation of one 600 mg Theophylline (Anhydrous) Extended-Release Tablet and one and one-half 400 mg Theophylline (Anhydrous) Extended-Release Tablets under fasted and fed conditions. The results of this 4-way randomized crossover study demonstrate the bioequivalence of the 400 mg and 600 mg Theophylline (Anhydrous) Extended-Release Tablets. Under fed conditions, the pharmacokinetic results for the one and one-half 400 mg tablets were AUC=214.64 ± 55.88 mcg hr/mL, Cmax=10.58 ± 2.21 mcg/mL and Tmax=9.00 ± 2.64 hours, and for the 600 mg tablet were AUC=207.85 ± 48.9 mcg hr/mL, Cmax=10.39 ± 1.91 mcg/mL and Tmax=9.58 ± 1.86 hours. Under fasted conditions the pharmacokinetic results for the one and one-half 400 mg tablets were AUC=191.85 ± 51.1 mcg hr/mL, Cmax=7.37 ± 1.83 mcg/mL and Tmax=8.08 ± 4.39 hours; and for the 600 mg tablet were AUC=199.39 ± 70.27 mcg hr/mL, Cmax=7.66 ± 2.09 mcg/mL and Tmax=9.67 ± 4.89 hours.

In this study the mean fed/fasted ratios for the one and one-half 400 mg tablets and the 600 mg tablet were about 112% and 104%, respectively.

In another study, the bioavailability of the 600 mg Theophylline (Anhydrous) Extended-Release Tablet was examined with morning and evening administration. This single-dose, crossover study in 22 healthy males was conducted under fed (standard high fat diet) conditions. The results demonstrated no clinically significant difference in the bioavailability of the 600 mg Theophylline (Anhydrous) Extended-Release Tablet administered in the morning or in the evening. The results were: AUC=233.6 ± 45.1 mcg hr/mL, Cmax=10.6 ± 1.3 mcg/mL and Tmax=12.5 ± 3.2 hours with morning dosing; AUC=209.8 ± 46.2 mcg hr/mL, Cmax=9.7 ± 1.4 mcg/mL and Tmax=13.7 ± 3.3 hours with evening dosing. The PMA/R ratio was 89.3%.

The absorption characteristics of Theophylline (Anhydrous) Extended-Release Tablets (theophylline, anhydrous) have been extensively studied. A steady-state crossover bioavailability study in 22 normal males compared two Theophylline (Anhydrous) Extended-Release 400 mg Tablets administered q24h at 8 a.m. immediately after breakfast with a reference controlled-release theophylline product administered BID in fed subjects at 8 a.m. immediately after breakfast and 8 p.m. immediately after dinner (769 calories, consisting of 97 grams carbohydrates, 33 grams protein and 27 grams fat). The pharmacokinetic parameters for Theophylline (Anhydrous) Extended-Release 400 mg Tablets under these steady-state conditions were AUC=203.3 ± 87.1 mcg hr/mL, Cmax=12.1 ± 3.8 mcg/mL, Cmin=4.50 ± 3.6, Tmax=8.8 ± 4.6 hours. For the reference BID product, the pharmacokinetic parameters were AUC=219.2 ± 88.4 mcg hr/mL, Cmax=11.0 ± 4.1 mcg/mL, Cmin=7.28 ± 3.5, Tmax=6.9 ± 3.4 hours. The mean percent fluctuation [(Cmax-Cmin/Cmin)100]=169% for the once daily regimen and 51% for the reference product BID regimen.

The bioavailability of the 600 mg Theophylline (Anhydrous) Extended-Release tablet was further evaluated in a multiple dose, steady-state study in 28 healthy males comparing the 600 mg Tablet to one and one-half 400 mg Theophylline (Anhydrous) Extended-Release Tablets. All subjects had previously established theophylline clearances of ≤4 L/hr and were dosed once-daily for 6 days under fed conditions. The results showed no clinically significant difference between the 600 mg and one and one-half 400 mg Theophylline (Anhydrous) Extended-Release tablet regimens. Steady-state results were:

|                          | 600 MG (ONE + ONE-HALF 400 MG TABLETS) FED | 600 MG TABLET FED |
|--------------------------|--|-------------------|
| AUC 0-24 hrs (mcg hr/mL) | 209.77 ± 51.04                             | 212.32 ± 56.29    |
| Cmax (mcg/mL)            | 12.91 ± 2.46                               | 13.17 ± 3.11      |
| Cmin (mcg/mL)            | 5.52 ± 1.79                                | 5.39 ± 1.95       |
| Tmax (hours)             | 8.62 ± 3.21                                | 7.23 ± 2.35       |
| Percent Fluctuation      | 183.73 ± 54.02                             | 179.72 ± 28.86    |

The bioavailability ratio for the 600/400 mg tablets was 98.8%. Thus, under all study conditions the 600 mg tablet is bioequivalent to one and one-half 400 mg tablets.

Studies demonstrate that as long as subjects were either consistently fed or consistently fasted, there is similar bioavailability with once-daily administration of Theophylline (Anhydrous) Extended-Release Tablets whether dosed in the morning or evening.

**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 0.3-0.7 L/kg) based on body weight. Theophylline passes freely across the placenta into the 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 (10-20 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 6-12 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 A2, while cytochromes P-450 2E1 and 450 3A3 catalyze the hydroxylation to 1,3-dimethyluric acid. Demethylation to 1-methylxanthine 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 <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 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 <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 (35-40%), 1-methyluric acid (20-25%) and 3-methylxanthine (15-20%). 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 >3 months of age. 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 30-65 hours (average 40 hours) in adults. At steady state, on a dosage regimen with 24-hour intervals, the expected mean trough concentration is approximately 50% 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 these patients administration of theophylline may be required more frequently (every 12 hours).

**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 (>60 years) 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. Signs of reduced theophylline clearance, however, have 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 >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 smoking and cessation of 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 non-smoking 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 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., >22 mcg/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.

**Contraindications** 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 is 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 (Anhydrous) Extended-Release Tablets is 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 that reduce 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 <1 year
- Elderly (>60 years)

### Concurrent Diseases

- Acute pulmonary edema
- Congestive heart failure
- Cor-pulmonale
- Fever; ≥102° for 24 hours or more; or lesser temperature elevations for longer periods
- Hypothyroidism
- Liver disease; cirrhosis, acute hepatitis
- Reduced renal function in infants <3 months of age
- Sepsis with multi-organ failure
- Shock

### Cessation of Smoking

### Drug Interactions

Adding a drug that inhibits theophylline metabolism (e.g., cimetidine, erythromycin, tacrine) or decreasing the currently 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).

