CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBERS:

89-822 & 89-823/S-001; S-002; S-004; S-005; S-008

Trade Name: Uni-Dur

Generic Name: Theophylline Extended-release Tablets

Sponsor: Key Pharmaceuticals, Inc.
Schering-Plough Corporation

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBERS: 89-822 & 89-823/ S-001; S-002; S-004; S-005; S-008

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBERS:

89-822 & 89-823/ S-001; S-002; S-004; S-005; S-008

APPROVAL LETTERS

ANDA 89-822/S-001 (400 mg)
89-823/S-001 (600 mg)

JAN 31 1995

Key Pharmaceuticals, Inc.
Schering-Plough Corporation
Attn: Richard N. Spivey
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Sir:

Reference is made to your supplemental new drug applications dated January 18, 1995, submitted pursuant to Section 314.70(c)(Special Supplement - Changes Being Effected) of the Regulations, regarding your abbreviated new drug applications for Uni-Dur® (Theophylline Extended-release Tablets).

The supplemental applications provide for revised package insert labeling to include changes in the PRECAUTIONS section.

We have completed the review of these supplemental applications and they are approved. Our letters of January 4, 1995, detailed the conditions relating to the approval of these abbreviated applications.

Please note that you have failed to submit a properly signed and executed 356(h) form. We refer you to 21 CFR 314.50(a) for further guidance.

The material submitted is being retained in our files.

Sincerely,

Jerry Phillips for /

1-31-95

Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDAs 89-822/S-002 (400 mg)
89-823/S-002 (600 mg)

MAY 12 1995

Schering-Plough Research Institute
Attention: Richard N. Spivey, Pharm.D., Ph.D.
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530

Dear Dr. Spivey:

This is in reference to your supplemental new drug applications dated March 20, 1995, submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug applications for Theophylline Extended-release Tablets, 400 mg and 600 mg.

Reference is also made to the telephone call between Schering-Plough and the Office of Generic Drugs (OGD) on April 27, 1995.

The supplemental applications provide for a change in the interim dissolution specifications specified in the January 4, 1995, approval letter.

We have completed the review of these supplemental applications and the following dissolution specifications are approved:

Time(hr)	Dissolution Range (%)
1	[redacted]
8	[redacted]
12	[redacted]
16	[redacted]
24	NLT [redacted]

The dissolution testing should be incorporated into the stability and quality control program using the same method as proposed in your application Please be advised that the first 3 commercial batches must be placed in the stability program as per the approved protocol. Schering-Plough is committed to:

1. Monitor the clinical performance of the product closely after products reach the market (post marketing surveillance).

2. Meet and or submit relevant data to OGD concerning the post marketing surveillance, stability, or any additional bioequivalence studies, related to the product, six-months after the product is placed in the market.

Schering-Plough is further advised that any post-approval changes where its determined by OGD that an *in vivo* study is required, the pivotal study required for approving such a change will be a single dose fasting study, not a multiple-dose study.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81. The material submitted is being retained in our files.

Sincerely yours,

Gordon R. Johnston for/ 5/12/95

Douglas L. Sporn
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 89-822/S-004 (400 mg)
89-823/S-004 (600 mg)

Schering Corporation
Attention: Joseph F. Lamendola
2000 Galloping Hill Road
Kenilworth, NJ 07033

JUN 18 1997

Dear Sir:

This is in reference to your supplemental new drug applications dated August 24, 1995, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug application for Uni-Dur® (Theophylline Extended-release Tablets).

Reference is also made to your amendments dated August 2, 1996 and April 1, 1997.

The supplemental applications provide for revised package insert labeling to include evening dosing with Uni-Dur® tablets and revisions throughout the text of the insert.

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

6/17/97

Roger L. Williams, M.D.
Deputy Center Director for
Pharmaceutical Science
Center for Drug Evaluation and Research

ANDA 89-822/S-005
89-823/S-005

Schering Corporation
Attention: Joseph F. Lamendola
2000 Galloping Hill Road
Kenilworth, NJ 07033

JUN 18 1997

Dear Sir:

This is in reference to your supplemental new drug applications dated October 25, 1996, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug applications for Uni-Dur® (Theophylline Extended-release Tablets).

Reference is also made to your amendments dated April 2, 1997 and April 30, 1997.

The supplemental applications provide for revised package insert labeling reflecting changes in the PRECAUTIONS section of the insert.

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

Jerry Phillips 6/17/97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 89-822/S-005 (400 mg)
89-823/S-005 (600 mg)

Schering Corporation
Attn: Joseph F. Lamendola
2000 Galloping Hill Road
Kenilworth, NJ 07033

FEB 18 1997

Dear Sir:

This is in reference to your supplemental new drug applications dated October 25, 1996, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug applications for Uni-Dur® (Theophylline Extended-release Tablets).

The supplemental applications provide for revised package insert labeling to include changes in the PRECAUTIONS, Drug Interactions subsection of the package insert.

Your proposed labeling revisions were forwarded to the Division of Pulmonary Drug Products (HFD-570) for their review and comment. After completion of their review of these supplemental applications they are approvable. However, before the supplemental applications may be approved it is necessary that you make the following revision:

PRECAUTIONS

Table II - Insert the following prior to "Rifampin":

Ritonavir	Increases theophylline clearance (mechanism unknown)	43% decrease in AUC

Submit final printed labeling as an amendment to each of these supplemental applications.

To facilitate review of your next submissions, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide side-by-side comparisons of your proposed labeling with your last submissions with all differences annotated and explained.

The changes provided for in these supplemental applications may not be initiated until you have been notified in writing that the supplemental applications are approved.

Sincerely yours,

John J. Grace for 2-18-97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 89-822/S-005 (400 mg)
89-823/S-005 (600 mg)
Division File
HFD-600/Reading File C.Holquist 2/18/97 J Grace 2/18/97
HFD-613/CHolquist/CHoppes/JGrace(no cc:) C Hoppes 2/18/97
HFD-610/JPhillips
njg/2/18/97/X:\NEW\FIRMSNZ\SCHERING\LTRS&REV\89822S05.AEL
Approvable Letter - Multiple Supplements

APPEARS THIS WAY
ON ORIGINAL

ANDA 89-822/S-008 (Uni-Dur 400 mg)
89-823/S-008 (Uni-Dur 600 mg)
85-328/S-048 (Theo-Dur 100 mg & 300 mg)
86-998/S-038 (Theo-Dur 200 mg)
89-131/S-023 (Theo-Dur 450 mg)

JAN 10 2002

Schering Corporation
Attn: Mr. Joseph F. Lamendola
2000 Galloping Hill Road
kenilworth, New Jersey 07033

Dear Sir:

This is in reference to your supplemental new drug applications dated March 29, 2001, submitted pursuant to 21 CFR 314.70(c)(Special Supplement - Changes Being Effected) regarding your abbreviated new drug applications for Theophylline Extended -Release Tablets.

The supplemental applications provide for revised draft package insert labeling reflecting the addition of "St.Johns Wort (Hypericum perforatum)" to the PRECAUTIONS, Information for Patients and Drug Interaction subsections.

We have completed the review of these supplemental applications and they are approved.

However, at the time of next printing, it is necessary that you make the following changes, then submit 12 copies of final print insert labeling as a Special Supplement - Changes Being Effected:

Information for Patients subsection - Delete the following paragraph:

[redacted]

And replace with the following:

> The dietary supplement St. John's Wort (Hypericum perforatum) should not be taken at the same time as theophylline, since it may result in decreased theophylline levels. If patients are already taking St. John's Wort and theophylline together, they should consult their physician before stopping the St. John's Wort, since their theophylline concentrations may rise when this is done, resulting in toxicity.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

John D Grace for 11-9-2002

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBERS:

89-822 & 89-823/S-001; S-002; S-004; S-005; S-008

FINAL PRINTED LABELING(S)

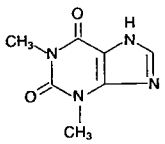
F-00000000

Some of the information contained in this insert (eg, information regarding pediatric patients under the age of 12) was derived from FDA's Class Labeling Guidance for Immediate-Release Theophylline Products and is intended for informational purposes only.

DESCRIPTION

UNI-DUR® Extended-release Tablets for oral administration contain 600 mg anhydrous theophylline in an extended-release system which allows a 24-hour dosing interval for appropriate patients.

Theophylline is a bronchodilator, structurally classified as a methylxanthine. It occurs as a white, odorless, crystalline powder with a bitter taste. Anhydrous theophylline has the chemical name 1*H*-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 $C_7H_8N_4O_2$ with a molecular weight of 180.17.

The inactive ingredients for UNI-DUR 600 mg Extended-release Tablets include: acacia, NF; cellulose acetate phthalate, NF; cetyl alcohol, NF; confectioners' sugar, NF; corn starch, NF; diethyl phthalate, NF; mono- and di-glycerides, NF; lactose monohydrate, NF; magnesium stearate, NF; myristyl alcohol, NF; sugar spheres, NF; and white wax, NF.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Theophylline has two distinct actions in the airways of patients with reversible obstruction; smooth muscle relaxation (ie, bronchodilation) and suppression of the response of the airways to stimuli (ie, nonbronchodilator prophylactic effects). While the mechanisms of action of theophylline are not known with certainty, studies in animals suggest that bronchodilation is mediated by the inhibition of two isozymes of phosphodiesterase (PDE III and, to a lesser extent, PDE IV) while nonbronchodilator 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 (eg, hypotension, tachycardia, headache, and emesis) and adenosine receptor antagonism (eg, 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 >10 mcg/mL, but patients with mild disease may benefit from lower concentrations. At serum theophylline concentrations >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 presystemic 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 coadministration 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 (eg, at 24-hour intervals) and periodically in patients receiving long-term therapy (eg, 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, Monitoring Serum Theophylline Concentrations** and **DOSAGE AND ADMINISTRATION**).

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)	
Age				
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 3-30 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 nonsmoking asthmatics	0.65	(0.27-1.03)	8.7	(6.1-12.8)
Elderly (>60 years)				
nonsmokers 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**	(3.1-8.2)
COPD >60 years, stable nonsmoker >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 multiorgan 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 1 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 nonlinear pharmacokinetics.

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

UNI-DUR Pharmacokinetics

Following the single-dose crossover administration of a 600 mg UNI-DUR Tablet to 20 healthy male subjects after an overnight fast, a peak serum theophylline concentration of 5.3 ± 1.3 mcg/mL was obtained at 13.6 ± 3.7 hours and the mean area under the curve extrapolated to infinity (AUC_{inf}) was 132.7 ± 45.1 mcg hr/mL. When taken immediately after a high-fat breakfast, the mean AUC_{inf} was 136.0 ± 36.7 mcg hr/mL with a mean peak theophylline serum level of 5.2 ± 1.5 mcg/mL at 17.1 ± 6.3 hours. While food did not affect the extent of absorption as evidenced by the similar AUC_{inf} values, food did prolong the time to peak concentration. The absorption from half tablets of the 600 mg product was also evaluated and found to be bioequivalent to that of the whole tablets. The relative extent of absorption of theophylline from the 600 mg UNI-DUR Tablet, fasting, when compared to an immediate-release theophylline tablet, was 84.3%, and for the nonfasting treatment was 88.7%.

In a separate multiple-dose, study, two 400 mg UNI-DUR Tablets were compared to one 600 mg UNI-DUR Tablet. This study was a two-way, randomized, crossover, multiple-dose study in 17 nonsmoking healthy males. Both products were dosed once a day in the morning after an overnight fast and 1 hour prior to a meal for 5 days. There was no significant difference in any of the pharmacokinetic parameters when corrected for dose. The mean dose AUC_{ss} (corrected to the 600 mg dose) for the two 400 mg UNI-DUR Tablets was 179.7 ± 62.9 mcg hr/mL and for the 600 mg UNI-DUR Tablet was 170.9 ± 75.2 mcg hr/mL. The two 400 mg UNI-DUR Tablets reached dose corrected maximum serum concentration of 9.8 ± 2.6 mcg/mL and the 600 mg UNI-DUR Tablet reached a maximum of 9.7 ± 3.5 mcg/mL. The minimum concentrations were 4.9 ± 2.6 mcg/mL and 4.4 ± 2.6 mcg/mL for the two 400 mg and 600 mg UNI-DUR Tablets, respectively.

Steady-state pharmacokinetics were determined in a multiple-dose, crossover study with 24 healthy nonsmoking male subjects having an average theophylline clearance of 5.70 ± 2.36 (S.D.) liters per hour. Following an overnight fast, a UNI-DUR 600 mg Extended-release Tablet was administered once daily in the morning for 5 consecutive days. The UNI-DUR Tablet exhibited better extended-release characteristics compared with a reference extended-release q12h product (2 x 300 mg) administered once daily in the morning following an overnight fast for 5 consecutive days. The results are noted as follows (mean values ± S.D.):

	AUC_{ss} (mcg hr/mL)	C_{max} (mcg/mL)	C_{min} (mcg/mL)	T_{max} (hr)
UNI-DUR	119±36	6.9±2.4	3.7±1.3	11.5±5.7
Reference	154±37	10.5±2.3	2.5±1.1	7.6±1.7

The mean percent fluctuation [$(C_{max}-C_{min}/C_{min}) \times 100$] was 130% for the once-daily UNI-DUR regimen and 389% for the reference q12h product administered once daily. The extent of theophylline absorption from UNI-DUR Tablets relative to the reference q12h product was 74.9% (95% C.I. = 67-84).

In a randomized, multiple-dose, crossover study with 18 healthy male subjects, a 600 mg UNI-DUR Extended-release Tablet was administered once daily either in the morning or evening for 5 consecutive days. The theophylline AUC_{ss} for the 24-hour period following the dose given on day 5 was equivalent for morning (177 ± 89 mcg hr/mL) and evening (175 ± 76 mcg hr/mL) administration. The peak theophylline concentrations (C_{max}) at steady state were also equivalent for morning (10.6 ± 4.9 mcg/mL) and evening (10.3 ± 4.0 mcg/mL) administration.

Steady-state pharmacokinetics comparing UNI-DUR Tablets once-daily administration with twice-daily administration were determined in a multiple-dose, crossover study with 24 healthy, nonsmoking male subjects having an average theophylline clearance of 4.53 ± 1.21 (S.D.) liters per hour. Using UNI-DUR 400 mg Extended-release Tablets, a total daily theophylline dose of 800 mg was administered for 5 consecutive days either once daily as two tablets in the morning (8 am) with a standardized breakfast or twice daily as one tablet in the morning (8 am) with a standardized breakfast and one tablet in the evening (8 pm). The once-daily UNI-DUR regimen was bioequivalent to the twice-daily UNI-DUR regimen. The results are noted as follows (mean values ± S.D.):

	AUC_{ss} (mcg hr/mL)	C_{max} (mcg/mL)	C_{min} (mcg/mL)	T_{max} (hr)
QD Regimen	187±45	10.4±2.9	6.0±1.3	12.0±3.7
q12h Regimen	187±43	9.4±2.2	8.4±2.6	14.5±6.6

The mean percent fluctuation [$(C_{max}-C_{min}/C_{min}) \times 100$] was 78% for the once-daily UNI-DUR regimen and 17% for the twice-daily UNI-DUR regimen. The extent of theophylline absorption from the once-daily UNI-DUR regimen relative to the twice-daily UNI-DUR regimen was 100% (95% C.I. = 95-105).

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 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 (10-20 mcg/mL) due to elevated concentrations of the pharmacologically active unbound drug. Similarly, a patient with decreased theophylline binding may have a subtherapeutic 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 1 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 P450 1A2, while cytochromes P450 2E1 and P450 3A3 catalyze the hydroxylation to 1,3-dimethyluric acid. Demethylation to 1-methylxanthine appears to be catalyzed either by cytochrome P450 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 1 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 N-demethylation and hydroxylation pathways of theophylline biotransformation are capacity-limited. Due to the wide intersubject variability of the rate of theophylline metabolism, nonlinearity of elimination may begin in some patients at serum theophylline concentrations <10 mcg/mL. Since this nonlinearity 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 V**). Accurate prediction of dose-dependency of theophylline metabolism in patients *a priori* is not possible, but patients with very high initial clearance rates (ie, 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 3 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 (ie, 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, 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 immediate-release 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 (8-12 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 (>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 1 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 3 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, eg, about 10%, of the administered theophylline dose is excreted unchanged in the urine of children greater than 3 months of age and adults. Since little theophylline is excreted unchanged in the urine and since active metabolites of theophylline (ie, 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 (eg, 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 appear 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 1 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 or lesser temperature elevations for longer periods are probably required to produce a clinically significant increase in serum theophylline concentrations. Children with rapid rates of theophylline clearance (ie, those who require a dose that is substantially larger than average [eg, <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
UNI-DUR Extended-release Tablets are indicated for the treatment of the symptoms and reversible airflow obstruction associated with chronic asthma and other chronic lung diseases, eg, emphysema and chronic bronchitis.

CONTRAINDICATIONS
UNI-DUR Extended-release Tablets are contraindicated in patients with a history of hypersensitivity to theophylline or other components in the product.

WARNINGS
Serious side effects such as ventricular arrhythmias, convulsions, or even death may appear as the first sign of toxicity without any recognized prior warnings. Less serious signs of theophylline toxicity (eg, nausea and restlessness) may occur frequently when initiating therapy but are usually transient. When such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 mcg/mL. Stated differently, serious toxicity is not reliably preceded by less severe side effects.

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 (peptic ulcer disease should be controlled with appropriate therapy since theophylline is known to increase peptic acid secretion)
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 so as to lower serum theophylline levels to within the therapeutic range 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°F 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 (eg, cimetidine, erythromycin, tacrine) or stopping a concurrently administered drug that enhances theophylline metabolism (eg, 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 should be 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, Dosage Guidelines, Table V**).

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 $beta_2$-selective agonists and systemically administered corticosteroids 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, Monitoring Serum Theophylline Concentrations**).

As the rate of theophylline clearance may be dose-dependent (ie, steady-state serum concentrations may increase disproportionately to the increase in dose), an increase in dose based upon a subtherapeutic 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 V**).

PRECAUTIONS
UNI-DUR Tablets SHOULD *NOT* BE CHEWED OR CRUSHED AND SHOULD *BE BROKEN ONLY AT THE SCORE.*

General:
Careful consideration of the various interacting drugs (including recently discontinued medications), physiologic conditions, and other factors such as smoking 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 IV**).

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 thegphylline 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 [eg, fever (see **CLINICAL PHARMACOLOGY**, *Fever*), 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—8 to 12 hours after a UNI-DUR dose at steady state. For most patients, steady state will be reached after 4 days of dosing with UNI-DUR Tablets 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 (ie, 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 12 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 (eg, 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-6 mg/dL), free fatty acids (from a mean of 451 μeq/L-800 μeq/L), total cholesterol (from a mean of 140 vs 160 mg/dL), HDL (from a mean of 36-50 mg/dL), HDL/LDL ratio (from a mean of 0.5-0.7), 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 1 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:

This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all adverse or intended effects.

The patient (or parent/caregiver) should be instructed to seek medical advice whenever nausea, vomiting, persistent headache, insomnia, restlessness, or rapid heartbeat 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 informed that theophylline interacts with a wide variety of drugs (see **Table II**). The herbal remedy St. John's Wort (Hypericum perforatum) should not be taken at the same time as theophylline. If they are already taking St. John's Wort they should consult their physician before stopping the St. John's Wort preparations. They 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.

UNI-DUR Tablets *should not be chewed or crushed.* Information relating to taking UNI-DUR Tablets in relation to meals or fasting should be provided.

Drug Interactions

Drug/Drug Interactions:

Theophylline interacts with a wide variety of drugs. The interaction may be pharmacodynamic, ie, 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, ie, 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 (eg, 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 (eg, 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 listing of drugs in Table II is 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 be required to achieve desired effect.
Alcohol	A single large dose of alcohol (eg, 3 mL/kg of whiskey) decreases theophylline clearance for up to 24 hours.	30% increase
Allopurinol	Decreases theophylline clearance at allopurinol doses ≥600 mg/day.	25% increase
Aminoglutethimide	Increases theophylline clearance by induction of microsomal enzyme activity.	25% decrease
Carbamazepine	Similar to aminoglutethimide.	30% decrease
Cimetidine	Decreases theophylline clearance by inhibiting cytochrome P450 1A2.	70% increase
Ciprofloxacin	Similar to cimetidine.	40% increase
Clarithromycin	Similar to erythromycin.	25% increase
Diazepam	Benzodiazepines increase CNS concentrations of adenosine, a potent CNS depressant, while theophylline blocks adenosine receptors.	Larger diazepam doses may be required to produce desired level of sedation. Discontinuation of theophylline without reduction of diazepam dose may result in respiratory depression.
Disulfiram	Decreases theophylline clearance by inhibiting hydroxylation 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 theophylline clearance by inhibiting cytochrome P450 3A3.	35% increase. Erythromycin steady-state serum concentrations decrease by a similar amount.
Estrogen	Estrogen-containing oral contraceptives decrease theophylline clearance in a dose-dependent fashion. The effect of progesterone on theophylline clearance is unknown.	30% increase
Flurazepam	Similar to diazepam.	Similar to diazepam.
Fluvoxamine	Similar to cimetidine.	Similar to cimetidine.
Halothane	Halothane sensitizes the myocardium to catecholamines; theophylline increases release of endogenous catecholamines.	Increased risk of ventricular arrhythmias.
Interferon, human recombinant alpha-A	Decreases theophylline clearance.	100% increase
Isoproterenol (IV)	Increases theophylline clearance.	20% decrease
Ketamine	Pharmacologic.	May lower theophylline seizure threshold.

Table II. Clinically significant drug interactions with theophylline.* *(cont.)*

Drug	Type of Interaction	Effect**
Lithium	Theophylline increases renal lithium clearance.	Lithium dose required to achieve a therapeutic serum concentration increased 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 greater effect.
Mexiletine	Similar to disulfiram.	80% increase
Midazolam	Similar to diazepam.	Similar to diazepam.
Moricizine	Increases theophylline clearance.	25% decrease
Norfloxacin	Increases serum theophylline levels.	
Ofloxacin	Increases serum theophylline levels.	
Pancuronium	Theophylline may antagonize non-depolarizing neuromuscular blockingeffects; possibly due to phosphodiesterase inhibition.	Larger dose of pancuronium may be required to achieve neuromuscular blockade.
Pentoxifylline	Decreases theophylline clearance.	30% increase
Phenobarbital (PB)	Similar to aminoglutethimide.	25% decrease after 2 weeks of concurrent PB.
Phenytoin	Phenytoin increases theophylline clearance by increasing microsomal enzyme activity. Theophylline decreases phenytoin absorption.	Serum theophylline and phenytoin concentrations decrease about 40%.
Propafenone	Decreases theophylline clearance and pharmacologic interaction.	40% increase. Beta2-blocking effect may decrease efficacy of theophylline.
Propranolol	Similar to cimetidine and pharmacologic interaction.	100% increase. Beta$_2$-blocking effect may decrease efficacy of theophylline.
Rifampin	Increases theophylline clearance by increasing cytochrome P450 1A2 and 3A3 activity.	20%-40% decrease
Ritonavir	Increases theophylline clearance (mechanism unknown).	43% decrease in AUC
St. John's Wort (Hypericum perforatum)	Decrease in theophylline plasma concentration.	
Sucralfate	Reduced absorption of theophylline.	
Sulfinpyrazone	Increases theophylline clearance by increasing demethylation and hydroxylation. Decreases renal clearance of theophylline.	20% decrease
Tacrine	Similar to cimetidine, also increases renal clearance of theophylline.	90% increase
Thiabendazole	Decreases theophylline clearance.	190% increase
Ticlopidine	Decreases theophylline clearance.	60% increase
Troleandomycin	Similar to erythromycin.	33%-100% increase depending on troleandomycin 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.

Drug/Food Interactions:
The extent of theophylline absorption from UNI-DUR Extended-release Tablets is similar when administered fasting or immediately after a high-fat content breakfast. However, the time to peak concentration was delayed following the high-fat content breakfast (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**). This breakfast contained 729 total kilocalories of which 55% were derived from 45 g of fat, and it consisted of two scrambled eggs, two strips of bacon, one slice of toast with 1 pat of butter, 3 oz. of hash brown potatoes, and 180 mL of whole milk. 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 (eg, cefazolin, cephalothin), however, may interfere with certain HPLC techniques. Caffeine and xanthine metabolites in 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 30-150 mg/kg) and rats (oral doses 5-75 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 B6C3F$_1$ mice at oral doses of 120, 270, and 500 mg/kg (approximately 1.0-3.0 times the human dose on a mg/m^2 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 B6C3F$_1$ mice at oral doses of 40 to 300 mg/kg (approximately 2.0 times the human dose on a mg/m^2 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 nonrodents (eg, 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 recommended human dose on a mg/m^2 basis or CD-1 rats at oral doses up to 260 mg/kg, approximately 3.0 times the recommended human dose on a mg/m^2 basis. At a dose of 220 mg/kg, embryo-toxicity 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:
Safety and effectiveness of UNI-DUR Extended-release Tablets in pediatric patients under 12 years of age have not been established. Other theophylline formulations, however, are safe and effective for the approved indications in pediatric patients under the age of 12. 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 IV**).

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 younge maximum daily dose of theophylline in patients greater than 60 years of age ordina unless the patient continues to be symptomatic and the peak steady-state ser <10 mcg/mL (see **DOSAGE AND ADMINISTRATION**). Theophylline doses gre prescribed with caution in elderly patients.

ADVERSE REACTIONS
Adverse reactions associated with theophylline are generally mild when peak seru <20 mcg/mL and mainly consist of transient caffeine-like adverse effects such as insomnia. When peak serum theophylline concentrations exceed 20 mcg/mL, how range of adverse reactions including persistent vomiting, cardiac arrhythmias, and lethal (see **OVERDOSAGE**). The transient caffeine-like adverse reactions occur theophylline therapy is initiated at doses higher than recommended initial doses >12 mg/kg/day in children beyond >1 year of age). During the initiation of theophy effects may transiently alter patient behavior, especially in school-age children. Initiation of theophylline therapy at a low dose with subsequent slow titratior maximum dose will significantly reduce the frequency of these transient adverse eff **TRATION, Table IV**). In a small percentage of patients (<3% of children and <10% effects persist during maintenance therapy, even at peak serum theophylline cor range (ie, 10-20 mcg/mL). Dosage reduction may alleviate the caffeine-like adverse persistent adverse effects should result in a reevaluation of the need for contir potential therapeutic benefit of alternative treatment.

Other adverse reactions that have been reported to occur at serum theophylline cc include diarrhea, irritability, restlessness, fine skeletal muscle tremors, alopecia, tions, rash, reflex hyperexcitability, transient diuresis, and ventricular arrhythmias. \ these reported events is not known. In patients with hypoxia secondary to COPI flutter have been reported at serum theophylline concentrations ≥ 15 mcg/mL. The of seizures at serum theophylline concentrations <20 mcg/mL in patients with an u elderly patients. The occurrence of seizures in elderly patients with serum theopt may be secondary to decreased protein binding resulting in a larger proportic concentration in the pharmacologically active unbound form. The clinical charact patients with serum theophylline concentrations <20 mcg/mL have generally be with excessive serum theophylline concentrations resulting from an overdose (ie, often stopped without anticonvulsant therapy, and did not result in neurological res

Table III. Manifestations of theophylline toxicity.*

Sign/Symptom	Percentage of patients reported v Acute Overdose (Large Single Ingestion) Study 1 (n=157)	Study 2 (n=14)
Asymptomatic	NR**	0
Gastrointestinal		
Vomiting	73	93
Abdominal pain	NR**	21
Diarrhea	NR**	0
Hematemesis	NR**	0
Metabolic/Other		
Hypokalemia	85	79
Hyperglycemia	98	NR**
Acid/base disturbance	34	21
Rhabdomyolysis	NR**	7
Cardiovascular		
Sinus tachycardia	100	86
Other supraventricular tachycardias	2	21
Ventricular premature beats	3	21
Atrial fibrillation or flutter	1	NR**
Multifocal atrial tachycardia	0	NR**
Ventricular arrhythmias with hemodynamic instability	7	14
Hypotension/shock	NR**	21
Neurologic		
Nervousness	NR**	64
Tremors	38	29
Disorientation	NR**	7
Seizures	5	14
Death	3	21

*These data are derived from two studies in patients with serum theophylline first study (Study #1–Shanon, *Ann Intern Med.* 1993;119:1161-67), data we consecutive cases of theophylline toxicity referred to a regional poison center (Study #2–Sessler, *Am J Med.* 1990;88:567-76), data were retrospectively c theophylline concentrations >30 mcg/mL among 6000 blood samples ot theophylline concentrations in three emergency departments. Differences i theophylline toxicity between the two studies may reflect sample selection as #1, 48% of the patients had acute intoxications versus only 10% in Study #2 results.

** NR = Not reported in a comparable manner.

OVERDOSAGE
General:
The chronicity and pattern of theophylline overdosage significantly influence management and outcome. There are two common presentations: (1) *acute ov* excessive dose (>10 mg/kg) as occurs in the context of an attempted suicide *chronic overdosage*, ie, ingestion of repeated doses that are excessive for the p The most common causes of chronic theophylline overdosage include patient prescribing of an excessive dose or a normal dose in the presence of factors phylline clearance, and increasing the dose in response to an exacerbation of s serum theophylline concentration to determine whether a dose increase is safe.

Severe toxicity from theophylline overdose is a relatively rare event. In one frequency of hospital admissions for chronic overdosage of theophylline v exposure. In another study, among 6000 blood samples obtained for measuren tion, for any reason, from patients treated in an emergency department, 7% we 3% were >30 mcg/mL. Approximately two thirds of the patients with serum th 30 mcg/mL range had one or more manifestations of toxicity while >90% of pat trations >30 mcg/mL were clinically intoxicated. Similarly, in other reports, ser principally at serum concentrations >30 mcg/mL.

Several studies have described the clinical manifestations of theophylline over factors that predict life-threatening toxicity. In general, patients who experienc experience seizures than patients who have experienced a chronic overdosag concentration is >100 mcg/mL. After a chronic overdosage, generalized seizure and death may occur at serum theophylline concentrations >30 mcg/mL. The dosage is more strongly correlated with the patient's age than the peak seru >60 years are at the greatest risk for severe toxicity and mortality after a chro

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 <10 mcg/mL (see **DOSAGE AND ADMINISTRATION**). Theophylline doses greater than 400 mg/day should be prescribed with caution in elderly patients.

ADVERSE REACTIONS

Adverse reactions associated with theophylline are generally mild when peak serum theophylline concentrations are <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 (eg, >300 mg/day in adults and >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 IV**). In a small percentage of patients (<3% of children and <10% of adults), the caffeine-like adverse effects persist during maintenance therapy, even at peak serum theophylline concentrations within the therapeutic range (ie, 10-20 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 to occur at serum theophylline concentrations less than 20 mcg/mL include diarrhea, irritability, restlessness, fine skeletal muscle tremors, alopecia, muscle twitching/spasms, palpitations, rash, reflex hyperexcitability, transient diuresis, and ventricular arrhythmias. Whether or not theophylline caused these reported events is not known. In patients with hypoxia secondary to COPD, multifocal atrial tachycardia and flutter have been reported at serum theophylline concentrations ≥ 15 mcg/mL. There have been a few isolated reports of seizures at serum theophylline concentrations <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 <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 <20 mcg/mL have generally been milder than seizures associated with excessive serum theophylline concentrations resulting from an overdose (ie, they have generally been transient, often stopped without anticonvulsant therapy, and did not result in neurological residua).

Table III.

Manifestations of theophylline toxicity.*

Sign/Symptom	Acute Overdose (Large Single Ingestion) Study 1 (n=157)	Acute Overdose (Large Single Ingestion) Study 2 (n=14)	Chronic Overdosage (Multiple Excessive Doses) Study 1 (n=92)	Chronic Overdosage (Multiple Excessive Doses) Study 2 (n=102)
Percentage of patients reported with sign or symptom				
Asymptomatic	NR**	0	NR**	6
Gastrointestinal				
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 with hemodynamic instability	7	14	40	0
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 >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 >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 (eg, 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*, ie, ingestion of a single large excessive dose (>10 mg/kg) as occurs in the context of an attempted suicide or isolated medication error, and (2) *chronic overdosage*, ie, 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 caregiver 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 >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 >90% of patients with serum theophylline concentrations >30 mcg/mL were clinically intoxicated. Similarly, in other reports, serious toxicity from theophylline is seen principally at serum concentrations >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 >100 mcg/mL. After a chronic overdosage, generalized seizures, life-threatening cardiac arrhythmias, and death may occur at serum theophylline concentrations >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 >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, eg, 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 III.**

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 >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 Concentration >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, eg, 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 30-60 minutes).

T 1 2 3 5 6 7

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UNI-DUR®
(theophylline)
Extended-release
Tablets

Key Pharmaceuticals, Inc.
Kenilworth, NJ 07033 USA

Rev. 0/00 B-00000000

Animal studies and case reports of theophylline overdose in humans 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, eg, patients with acute overdoses and serum theophylline concentrations >100 mcg/mL or chronic overdosage in patients >60 years of age with serum theophylline concentrations >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 (eg, transfer of a high-risk patient from one healthcare facility to another for extracorporeal removal) and clinical circumstances that significantly interfere with efforts to enhance theophylline clearance (eg, 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 (ie, markedly increases the LD_{50}). 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 1-2 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, eg, 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 theophyllinelevel 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 (eg, 0.5 mg/kg up to 20 g, every 2 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 >20 <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 ensure that the concentration is not increasing.

B. Serum Concentration >30 <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 >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 >20 <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 ensure that the concentration is not increasing.

B. Serum Concentration >30 mcg/mL in patients <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 >30 mcg/mL in patients ≥ 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

The extent of absorption of theophylline from UNI-DUR Tablets when administered fasting or immediately after a high-fat content breakfast is similar. However, the time to peak concentration is delayed (see **PRECAUTIONS, Drug/Food Interactions**).

Effective use of theophylline (ie, the concentration of drug in the serum associated with optimal benefit and minimal risk of toxicity) is considered to occur when the theophylline concentration is maintained from 10 to 15 mcg/mL.

Patients who clear theophylline normally or relatively slowly, eg, nonsmokers, may be reasonable candidates for taking UNI-DUR Tablets once daily. However, certain patients, such as the young, smokers, and some nonsmoking adults are likely to metabolize theophylline more rapidly and may require dosing at 12-hour intervals. Such patients may experience symptoms of bronchospasm toward the end of a once-daily dosing interval and/or require a higher daily dose (higher than those recommended in labeling) and are more likely to experience relatively wide peak to trough differences in serum theophylline concentrations.

UNI-DUR Tablets may be administered either in the morning or in the evening.

UNI-DUR Tablets *should not be chewed or crushed.*

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 (eg, 400-1600 mg/day in adults <60 years old and 10-36 mg/kg/day in children 1-9 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/day in adults <60 years or 22 mg/kg/day in children 1 to 9 years, the steady-state peak serum theophylline concentration will be <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 IV**). 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, Monitoring Serum Theophylline Concentrations, and DOSAGE AND ADMINISTRATION, Table V**). Healthcare providers should instruct patients and caregivers 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, eg, every 24 hours.

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

Table IV contains theophylline dosing titration schema recommended for patients in various age groups and clinical circumstances. **Table V** 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 dose adjustments in order to decrease the risk of potentially serious adverse events associated with unexpected large increases in serum theophylline concentration.**

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

A. Children (12-15 years) and adults (16-60 years) without risk factors for impaired clearance.

Titration Step	*Children <45 kg*	*Children >45 kg and adults*
1. Starting dosage:	12-14 mg/kg/day up to a maximum of 300 mg/day administered QD*	300-400 mg/day† administered QD*
2. After 3 days, *if tolerated,* increase dose to:	16 mg/kg/day up to a maximum of 400 mg/day administered QD*	400-600 mg/day† administered QD*
3. After 3 more days, *if tolerated,* increase dose to:	20 mg/kg/day up to a maximum of 600 mg/day administered QD*	As with all theophylline products, doses greater than 600 mg should be titrated according to blood level (see **Table V**).

B. **Patients wth Risk Factors for Impaired Clearance, the Elderly (>60 Years), and Those in Whom it is Not Feasible to Monitor Serum Theophylline Concentrations:**

In children 12 to 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 ≥16 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 12 hours) to prevent breakthrough symptoms resulting from low trough concentrations before the next dose.

† If caffeine-like adverse effects occur, then consideration should be given to a lower dose and titrating the dose more slowly (see **ADVERSE REACTIONS**).

Table V. Dosage adjustment guided by serum theophylline concentration.

Peak Serum Concentration	Dosage Adjustment
<9.9 mcg/mL	If symptoms are not controlled and current dosage is tolerated, increase dose about 25%. Recheck serum concentration after 3 days for further dosage adjustment.
10-14.9 mcg/mL	If symptoms are controlled and current dosage is tolerated, maintain dose and recheck serum concentration at 6- to 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.¶
20-24.9 mcg/mL	Decrease dose by 25% even if no adverse 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).
>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 (eg, sustained fever), or a drug that interacts with theophylline is added or discontinued (see **WARNINGS**).

HOW SUPPLIED

UNI-DUR Extended-release Tablets are supplied as controlled-release tablets containing 600 mg of theophylline anhydrous. They are mottled white, capsule-shaped tablets, scored on one side and debossed with the product name and strength on the other.

UNI-DUR Extended-release Tablets 600 mg are available in bottles of 100 (NDC 0085-0814-01).

STORAGE CONDITIONS

Keep bottles tightly closed. Store between 15° and 25°C (59° and 77°F).

Rx only

Table II. Clinically significant drug interactions with theophylline.* *(cont.)*

Drug	Type of Interaction	Effect**
Norfloxacin	Increases serum theophylline levels.	
Ofloxacin	Increases serum theophylline levels.	
Pancuronium	Theophylline may antagonize non-depolarizing neuromuscular blocking effects; possibly due to phospho-diesterase inhibition.	Larger dose of pancuronium may be required to achieve neuromuscular blockade.
Pentoxifylline	Decreases theophylline clearance.	30% increase
Phenobarbital (PB)	Similar to aminoglutethimide.	25% decrease after 2 weeks of concurrent PB.
Phenytoin	Phenytoin increases theophylline clearance by increasing microsomal enzyme activity. Theophylline decreases phenytoin absorption.	Serum theophylline *and* phenytoin concentrations decrease about 40%.
Propafenone	Decreases theophylline clearance and pharmacologic interaction.	40% increase. $Beta_2$-blocking effect may decrease efficacy of theophylline.
Propranolol	Similar to cimetidine and pharmacologic interaction.	100% increase. $Beta_2$-blocking effect may decrease efficacy of theophylline.
Rifampin	Increases theophylline clearance by increasing cytochrome P450 1A2 and 3A3 activity.	20%-40% decrease
Sucralfate	Reduced absorption of theophylline.	
Sulfinpyrazone	Increases theophylline clearance by increasing demethylation and hydroxylation. Decreases renal clearance of theophylline.	20% decrease
Tacrine	Similar to cimetidine, also increases renal clearance of theophylline.	90% increase
Thiabendazole	Decreases theophylline clearance.	190% increase
Ticlopidine	Decreases theophylline clearance.	60% increase
Troleandomycin	Similar to erythromycin.	33%-100% increase depending on troleandomycin 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.

Drug/Food Interactions:
The extent of theophylline absorption from UNI-DUR® Extended-release Tablets is similar when administered fasting or immediately after a high-fat content breakfast. However, the time to peak concentration was delayed following the high-fat content breakfast (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**). This breakfast contained 729 total kilocalories of which 55% were derived from 45 g of fat; and it consisted of two scrambled eggs, two strips of bacon, one slice of toast with 1 pat of butter, 3 oz. of hash brown potatoes, and 180 mL of whole milk. 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 (eg, cefazolin, cephalothin), however, may interfere with certain HPLC techniques. Caffeine and xanthine metabolites in 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 30-150 mg/kg) and rats (oral doses 5-75 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 $B6C3F_1$ mice at oral doses of 120, 270, and 500 mg/kg (approximately 1.0-3.0 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 $B6C3F_1$ mice at oral doses of 40-300 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 nonrodents (eg, 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 recommended human dose on a mg/m² basis or 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 10-20 mcg/mL of theophylline a day is likely to receive 10-20 mg of theophylline per day. Serious adverse effects in the infant are unlikely unless the mother has toxic serum theophylline concentrations.

Pediatric Use:
Safety and effectiveness of UNI-DUR Extended-release Tablets in pediatric patients under 12 years of age have not been established. Other theophylline formulations, however, are safe and effective for the approved indications in pediatric patients under the age of 12. 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 IV**).

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 <10 mcg/mL (see **DOSAGE AND ADMINISTRATION**). Theophylline doses greater than 400 mg/day should be prescribed with caution in elderly patients.

ADVERSE REACTIONS
Adverse reactions associated with theophylline are generally mild when peak serum theophylline concentrations are <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 (eg, >300 mg/day in adults and >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 IV**). In a small percentage of patients (<3% of children and <10% of adults), the caffeine-like adverse effects persist during maintenance therapy, even at peak serum theophylline concentrations within the therapeutic range (ie, 10-20 mcg/mL). Dosage reduction may alleviate the caffeine-like adverse effects in these patients; however, persistent adverse effects should result in a re-evaluation of the need for continued theophylline therapy and the potential therapeutic benefit of alternative treatment.

Other adverse reactions that have been reported to occur at serum theophylline concentrations less than 20 mcg/mL include diarrhea, irritability, restlessness, fine skeletal muscle tremors, alopecia, muscle twitching/spasms, palpitations, rash, reflex hyperexcitability, transient diuresis, and ventricular arrhythmias. Whether or not theophylline caused these reported events is not known. In patients with hypoxia secondary to COPD, multifocal atrial tachycardia and flutter have been reported at serum theophylline concentrations ≥ 15 mcg/mL. There have been a few isolated reports of seizures at serum theophylline concentrations <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 <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 <20 mcg/mL have generally been milder than seizures associated with excessive serum theophylline concentrations resulting from an overdose (ie, they have generally been transient, often stopped without anticonvulsant therapy, and did not result in neurological residua).

Table III. Manifestations of theophylline toxicity.*

Sign/Symptom	Acute Overdose (Large Single Ingestion) Study 1 (n=157)	Acute Overdose (Large Single Ingestion) Study 2 (n=14)	Chronic Overdosage (Multiple Excessive Doses) Study 1 (n=92)	Chronic Overdosage (Multiple Excessive Doses) Study 2 (n=102)
Asymptomatic	NR**	0	NR**	6
Gastrointestinal				
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 with hemodynamic instability	7	14	40	0
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 >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 >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 (eg, 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,* ie, ingestion of a single large excessive dose (>10 mg/kg) as occurs in the context of an attempted suicide or isolated medication error, and (2) *chronic overdosage,* ie, 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 caregiver 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 20-30 mcg/mL range and 3% were >30 mcg/mL. Approximately two thirds of the patients with serum theophylline concentrations in the 20-30 mcg/mL range had one or more manifestations of toxicity while >90% of patients with serum theophylline concentrations >30 mcg/mL were clinically intoxicated. Similarly, in other reports, serious toxicity from theophylline is seen principally at serum concentrations >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 >100 mcg/mL. After a chronic overdosage, generalized seizures, life-threatening cardiac arrhythmias, and death may occur at serum theophylline concentrations >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 >60 years are at the greatest risk for severe toxicity and mortality after a chronic overdosage. Pre-existing or concurrent disease may also significantly increase the susceptibility of a patient to a particular toxic manifestation, eg, 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 III**.

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 >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 >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, eg, diazepam, in increments of 0.1-0.2 mg/kg every 1-3 minutes until seizures are terminated. Repetitive seizures should be treated with a loading dose of phenobarbital (20 mg/kg infused over 30-60 minutes). Animal studies and case reports of theophylline overdose in humans 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, eg, patients with acute overdoses and serum theophylline concentrations >100 mcg/mL or chronic overdosage in patients >60 years of age with serum theophylline concentrations >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 (eg, transfer of a high-risk patient from one healthcare facility to another for extracorporeal removal) and clinical circumstances that significantly interfere with efforts to enhance theophylline clearance (eg, 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 (ie, markedly increases the LD_{50}). 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 1-2 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, 2-4 hours later, and then at sufficient intervals, eg, 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 (eg, 0.5 mg/kg up to 20 g, every 2 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 >20 <30 mcg/mL
1. Administer a single dose of oral activated charcoal.
2. Monitor the patient and obtain a serum theophylline concentration in 2-4 hours to ensure that the concentration is not increasing.

B. Serum Concentration >30 <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 2-4 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 >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 2-4 hours to gauge the effectiveness of therapy and to guide further treatment decisions.

Chronic Overdosage

A. Serum Concentration >20 <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 2-4 hours to ensure that the concentration is not increasing.

B. Serum Concentration >30 mcg/mL in patients <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 2-4 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 >30 mcg/mL in patients ≥ 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 2-4 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 5-10 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.

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1165

UNI-DUR®
(theophylline)
Extended-release
Tablets

Key Pharmaceuticals, Inc.
Kenilworth, NJ 07033 USA

Rev. 3/97

DOSAGE AND ADMINISTRATION

The extent of absorption of theophylline from UNI-DUR Tablets when administered fasting or immediately after a high-fat content breakfast is similar. However, the time to peak concentration is delayed (see **PRECAUTIONS, Drug/Food Interactions**).

Effective use of theophylline (ie, the concentration of drug in the serum associated with optimal benefit and minimal risk of toxicity) is considered to occur when the theophylline concentration is maintained from 10 to 15 mcg/mL.

Patients who clear theophylline normally or relatively slowly, eg, nonsmokers, may be reasonable candidates for taking UNI-DUR Tablets once daily. However, certain patients, such as the young, smokers, and some nonsmoking adults are likely to metabolize theophylline more rapidly and may require dosing at 12-hour intervals. Such patients may experience symptoms of bronchospasm toward the end of a once-daily dosing interval and/or require a higher daily dose (higher than those recommended in labeling) and are more likely to experience relatively wide peak to trough differences in serum theophylline concentrations.

UNI-DUR Tablets may be administered either in the morning or in the evening.

UNI-DUR Tablets *should not be chewed or crushed.*

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 10-20 mcg/mL range varies fourfold among otherwise similar patients in the absence of factors known to alter theophylline clearance (eg, 400-1600 mg/day in adults <60 years old and 10-36 mg/kg/day in children 1-9 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/day in adults <60 years or 22 mg/kg/day in children 1-9 years, the steady-state peak serum theophylline concentration will be <10 mcg/mL in about 30% of patients, 10-20 mcg/mL in about 50%, and 20-30 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 IV**). 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, Monitoring Serum Theophylline Concentrations,** and **DOSAGE AND ADMINISTRATION, Table V**). Healthcare providers should instruct patients and caregivers 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, eg, every 24 hours.

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

Table IV contains theophylline dosing titration schema recommended for patients in various age groups and clinical circumstances. **Table V** 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 dose adjustments in order to decrease the risk of potentially serious adverse events associated with unexpected large increases in serum theophylline concentration.**

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

A. Children (12-15 years) and adults (16-60 years) without risk factors for impaired clearance.

Titration Step	*Children <45 kg*	*Children >45 kg and adults*
1. Starting dose†	12-14 mg/kg/day up to a maximum of 300 mg/day administered QD*	300-400 mg/day† administered QD*
2. After 3 days, *if tolerated,* increase dose to:	16 mg/kg/day up to a maximum of 400 mg/day administered QD*	400-600 mg/day† administered QD*
3. After 3 more days, *if tolerated,* increase dose to:	20 mg/kg/day up to a maximum of 600 mg/day administered QD*	As with all theophylline products, doses greater than 600 mg should be titrated according to blood level (see **Table V**).

B. **Patients With Risk Factors For Impaired Clearance, The Elderly (>60 Years), And Those In Whom It Is Not Feasible To Monitor Serum Theophylline Concentrations:**

In children 12-15 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 ≥16 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 12 hours) to prevent breakthrough symptoms resulting from low trough concentrations before the next dose.

†If caffeine-like adverse effects occur, then consideration should be given to a lower dose and titrating the dose more slowly (see **ADVERSE REACTIONS**).

Table V. Dosage adjustment guided by serum theophylline concentration.

Peak Serum Concentration	Dosage Adjustment
<9.9 mcg/mL	If symptoms are not controlled and current dosage is tolerated, increase dose about 25%. Recheck serum concentration after 3 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- to 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.¶
20-24.9 mcg/mL	Decrease dose by 25% even if no adverse 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).
>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 (eg, sustained fever), or a drug that interacts with theophylline is added or discontinued (see **WARNINGS**).

HOW SUPPLIED

UNI-DUR Extended-release Tablets are supplied as controlled-release tablets containing either 400 mg or 600 mg of theophylline anhydrous. They are mottled white, capsule-shaped tablets; scored on one side and debossed with the product name and strength on the other.

UNI-DUR Extended-release Tablets 400 mg are available in bottles of 100's (NDC 0085-0694-01).

UNI-DUR Extended-release Tablets 600 mg are available in bottles of 100's (NDC 0085-0814-01).

STORAGE CONDITIONS

Keep bottles tightly closed. Store between 15° and 25°C (59° and 77°F).

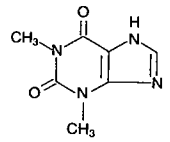
CAUTION: Federal law prohibits dispensing without prescription.

Some of the information contained in this insert (eg, information regarding pediatric patients under the age of 12) was derived from FDA's Class Labeling Guidance for Immediate-Release Theophylline Products and is intended for informational purposes only.

DESCRIPTION

UNI-DUR® Extended-release Tablets for oral administration contain 400 or 600 mg anhydrous theophylline in an extended-release system which allows a 24-hour dosing interval for appropriate patients.

Theophylline is a bronchodilator, structurally classified as a methylxanthine. It occurs as a white, odorless, crystalline powder with a bitter taste. Anhydrous theophylline has the chemical name 1*H*-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 $C_7H_8N_4O_2$ with a molecular weight of 180.17.

The inactive ingredients for UNI-DUR 400 and 600 mg Extended-release Tablets include: acacia, NF; acetone; cellulose acetate phthalate, NF; cetyl alcohol, NF; confectioner's sugar, NF; corn starch, NF; diethyl phthalate, NF; glyceryl monostearate; lactose monohydrate, NF; magnesium stearate, NF; myristyl alcohol, NF; nonpareil seeds (sugar spheres), NF; and white wax, NF.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Theophylline has two distinct actions in the airways of patients with reversible obstruction; smooth muscle relaxation (ie, bronchodilation) and suppression of the response of the airways to stimuli (ie, non-bronchodilator prophylactic effects). While the mechanisms of action of theophylline are not known with certainty, studies in animals suggest that bronchodilation is mediated by the inhibition of two isozymes of phosphodiesterase (PDE III 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 (eg, hypotension, tachycardia, headache, and emesis) and adenosine receptor antagonism (eg, 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 >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 coadministration 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 (eg, at 24-hour intervals) and periodically in patients receiving long-term therapy (eg, 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, Monitoring Serum Theophylline Concentrations** and **DOSAGE AND ADMINISTRATION**).

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)
Age		
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 3-30 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 nonsmoking asthmatics	0.65 (0.27-1.03)	8.7 (6.1-12.8)
Elderly (>60 years)		
nonsmokers 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 nonsmoker >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)

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 1 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 nonlinear pharmacokinetics.

† Reported range or estimated range (mean ± 2 S.D.) 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, parenteral nutrition, and daily consumption of charcoal-broiled beef. A high-carbohydrate/low-protein diet can decrease clearance and prolong the half-life of theophylline.

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

UNI-DUR Pharmacokinetics

Following the single-dose crossover administration of a 600 mg UNI-DUR Tablet to 20 healthy male subjects after an overnight fast, a peak serum theophylline concentration of 5.3 ± 1.3 mcg/mL was obtained at 13.6 ± 3.7 hours and the mean area under the curve extrapolated to infinity (AUC_{inf}) was 132.7 ± 45.1 mcg hr/mL. When taken immediately after a high-fat breakfast, the mean AUC_{inf} was 136.0 ± 36.7 mcg hr/mL with a mean peak theophylline serum level of 5.2 ± 1.5 mcg/mL at 17.1 ± 6.3 hours. While food did not affect the extent of absorption as evidenced by the similar AUC_{inf} values, food did prolong the time to peak concentration. The absorption from half tablets of the 600 mg product was also evaluated and found to be bioequivalent to that of the whole tablets. The relative extent of absorption of theophylline from the 600 mg UNI-DUR Tablet, fasting, when compared to an immediate-release theophylline tablet, was 84.3%; and for the nonfasting treatment was 88.7%.

In a separate multiple-dose study, two 400 mg UNI-DUR Tablets were compared to one 600 mg UNI-DUR Tablet. This study was a two-way, randomized, crossover multiple-dose study in 17 nonsmoking healthy males. Both products were dosed once a day in the morning after an overnight fast and 1 hour prior to a meal for 5 days. There was no significant difference in any of the pharmacokinetic parameters when corrected for dose.

The mean dose AUC_{ss} (corrected to the 600 mg dose) for the two 400 mg UNI-DUR Tablets was 179.7 ± 62.9 mcg hr/mL and for the 600 mg UNI-DUR Tablet was 170.9 ± 75.2 mcg hr/mL. The two 400 mg UNI-DUR Tablets reached dose corrected maximum serum concentration of 9.8 ± 2.6 mcg/mL and the 600 mg UNI-DUR Tablet reached a maximum of 9.7 ± 3.5 mcg/mL. The minimum concentrations were 4.9 ± 2.6 mcg/mL and 4.4 ± 2.6 mcg/mL for the two 400 mg and 600 mg UNI-DUR Tablets, respectively.

Steady-state pharmacokinetics were determined in a multiple-dose, crossover study with 24 healthy nonsmoking male subjects having an average theophylline clearance of 5.70 ± 2.36 (S.D.) liters per hour. Following an overnight fast, a UNI-DUR 600 mg Extended-release Tablet was administered once daily in the morning for 5 consecutive days. The UNI-DUR Tablet exhibited better extended-release characteristics compared with a reference extended-release q12h product (2 x 300 mg) administered once daily in the morning following an overnight fast for 5 consecutive days. The results are noted as follows (mean values ± S.D.):

	AUC_{ss} (mcg hr/mL)	C_{max} (mcg/mL)	C_{min} (mcg/mL)	T_{max} (hr)
UNI-DUR	119 ± 36	6.9 ± 2.4	3.7 ± 1.3	11.5 ± 5.7
Reference	154 ± 37	10.5 ± 2.3	2.5 ± 1.1	7.6 ± 1.7

The mean percent fluctuation [(C_{max}-C_{min}/C_{min}) x 100] was 130% for the once-daily UNI-DUR regimen and 389% for the reference q12h product administered once daily. The extent of theophylline absorption from UNI-DUR Tablets relative to the reference q12h product was 74.9% (95% C.I. = 67-84).

In a randomized, multiple-dose crossover study with 18 healthy male subjects, a 600 mg UNI-DUR Extended-release Tablet was administered once daily either in the morning or evening for 5 consecutive days. The theophylline AUC_{ss} for the 24-hour period following the dose given on day 5 was equivalent for morning (177 ± 89 mcg hr/mL) and evening (175 ± 76 mcg hr/mL) administration. The peak theophylline concentrations (C_{max}) at steady state were also equivalent for morning (10.6 ± 4.9 mcg/mL) and evening (10.3 ± 4.0 mcg/mL) administration.

Steady-state pharmacokinetics comparing UNI-DUR Tablets once-daily administration with twice-daily administration were determined in a multiple-dose, crossover study with 24 healthy, nonsmoking male subjects having an average theophylline clearance of 4.53 ± 1.21 (S.D.) liters per hour. Using UNI-DUR 400 mg Extended-release Tablets, a total daily theophylline dose of 800 mg was administered for 5 consecutive days either once daily as two tablets in the morning (8 AM) with a standardized breakfast or twice daily as one tablet in the morning (8 AM) with a standardized breakfast or twice daily as one tablet in the morning (8 AM) with a standardized breakfast and one tablet in the evening (8 PM). The once-daily UNI-DUR regimen was bioequivalent to the twice-daily UNI-DUR regimen. The results are noted as follows (mean values ± S.D.):

	AUC_{ss} (mcg hr/mL)	C_{max} (mcg/mL)	C_{min} (mcg/mL)	T_{max} (hr)
QD Regimen	187 ± 45	10.4 ± 2.9	6.0 ± 1.3	12.0 ± 3.7
q12h Regimen	187 ± 43	9.4 ± 2.2	8.4 ± 2.6	14.5 ± 6.6

The mean percent fluctuation [(C_{max}-C_{min}/C_{min}) x 100] was 78% for the once-daily UNI-DUR regimen and 17% for the twice-daily UNI-DUR regimen. The extent of theophylline absorption from the once-daily UNI-DUR regimen relative to the twice-daily UNI-DUR regimen was 100% (95% C.I. = 95-105).

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 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 (10-20 mcg/mL) due to elevated concentrations of the pharmacologically active unbound drug. Similarly, a patient with decreased theophylline binding may have a subtherapeutic 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 1 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 P450 1A2, while cytochromes P450 2E1 and P450 3A3 catalyze the hydroxylation to 1,3-dimethyluric acid. Demethylation to 1-methylxanthine appears to be catalyzed either by cytochrome P450 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 1 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 N-demethylation and hydroxylation pathways of theophylline biotransformation are capacity-limited. Due to the wide intersubject variability of the rate of theophylline metabolism, nonlinearity of elimination may begin in some patients at serum theophylline concentrations <10 mcg/mL. Since this nonlinearity 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 V**). Accurate prediction of dose-dependency of theophylline metabolism in patients *a priori* is not possible, but patients with very high initial clearance rates (ie, 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 3 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 (ie, 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, 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 immediate-release theophylline, steady state is reached in 30-65 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 4-5 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 (8-12 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 (>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 1 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 3 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, eg, about 10%, of the administered theophylline dose is excreted unchanged in the urine of children greater than 3 months of age and adults. Since little theophylline is excreted unchanged in the urine and since active metabolites of theophylline (ie, 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 (eg, 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 appear 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 1 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 or lesser temperature elevations for longer periods, are probably required to produce a clinically significant increase in serum theophylline concentrations. Children with rapid rates of theophylline clearance (ie, those who require a dose that is substantially larger than average [eg, >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

UNI-DUR Extended-release Tablets are indicated for the treatment of the symptoms and reversible airflow obstruction associated with chronic asthma and other chronic lung diseases, eg, emphysema and chronic bronchitis.

CONTRAINDICATIONS

UNI-DUR Extended-release Tablets are contraindicated in patients with a history of hypersensitivity to theophylline or other components in the product.

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UNI-DUR Extended-release Tablets are contraindicated in patients with a history of hypersensitivity to theophylline or other components in the product.

WARNINGS

Serious side effects such as ventricular arrhythmias, convulsions, or even death may appear as the first sign of toxicity without any recognized prior warnings. Less serious signs of theophylline toxicity (eg, nausea and restlessness) may occur frequently when initiating therapy but are usually transient. When such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 mcg/mL. Stated differently, serious toxicity is not reliably preceded by less severe side effects.

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 (peptic ulcer disease should be controlled with appropriate therapy since theophylline is known to increase peptic acid secretion)
- 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 so as to lower serum theophylline levels to within the therapeutic range 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°F 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 (eg, cimetidine, erythromycin, tacrine) or stopping a concurrently administered drug that enhances theophylline metabolism (eg, 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 should be 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, Dosage Guidelines, Table V**).

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 $beta_2$-selective agonists and systemically administered corticosteroids 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, Monitoring Serum Theophylline Concentrations**).

As the rate of theophylline clearance may be dose-dependent (ie, steady-state serum concentrations may increase disproportionately to the increase in dose), an increase in dose based upon a subtherapeutic 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 V**).

PRECAUTIONS

UNI-DUR TABLETS SHOULD *NOT* BE CHEWED OR CRUSHED AND SHOULD *BE BROKEN ONLY AT THE SCORE.*

General:

Careful consideration of the various interacting drugs (including recently discontinued medications), physiologic conditions, and other factors such as smoking 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 IV**).

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 [eg, fever (see **CLINICAL PHARMACOLOGY,** *Fever*), 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; 8 to 12 hours after a UNI-DUR dose at steady state. For most patients, steady state will be reached after 4 days of dosing with UNI-DUR Tablets 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 (ie, 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 12 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 (eg, 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 6-12 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 10-20 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 μeq/L to 800 μeq/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 uri
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Table II.

Drug	
Adenosine	
Alcohol	
Allopurinol	
Aminoglutethimi	
Carbamazepine	
Cimetidine	
Ciprofloxacin	
Clarithromycin	
Diazepam	
Disulfiram	
Enoxacin	
Ephedrine	
Erythromycin	
Estrogen	
Flurazepam	
Fluvoxamine	
Halothane	
Interferon, humar recombinant alph	
Isoproterenol (IV)	
Ketamine	
Lithium	
Lorazepam	
Methotrexate (MT	
Mexiletine	
Midazolam	
Moricizine	

WARNINGS

Serious side effects such as ventricular arrhythmias, convulsions, or even death may appear as the first sign of toxicity without any recognized prior warnings. Less serious signs of theophylline toxicity (eg, nausea and restlessness) may occur frequently when initiating therapy but are usually transient. When such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 mcg/mL. Stated differently, serious toxicity is not reliably preceded by less severe side effects.

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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:

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- 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 so as to lower serum theophylline levels to within the therapeutic range 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°F 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 (eg, cimetidine, erythromycin, tacrine) or stopping a concurrently administered drug that enhances theophylline metabolism (eg, 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 should be 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, Dosage Guidelines, Table V**).

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 $beta_2$-selective agonists and systemically administered corticosteroids 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, Monitoring Serum Theophylline Concentrations**).

As the rate of theophylline clearance may be dose-dependent (ie, steady-state serum concentrations may increase disproportionately to the increase in dose), an increase in dose based upon a subtherapeutic 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 V**).

PRECAUTIONS

UNI-DUR TABLETS SHOULD *NOT* BE CHEWED OR CRUSHED AND SHOULD *BE BROKEN ONLY AT THE SCORE.*

General:

Careful consideration of the various interacting drugs (including recently discontinued medications), physiologic conditions, and other factors such as smoking 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 IV**).

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 [eg, fever (see **CLINICAL PHARMACOLOGY, *Fever***), 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; 8 to 12 hours after a UNI-DUR dose at steady state. For most patients, steady state will be reached after 4 days of dosing with UNI-DUR Tablets 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 (ie, 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 12 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 (eg, 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 6-12 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 10-20 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 μeq/L to 800 μeq/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 10-20 mcg/mL range may also transiently decrease serum concentrations of triiodothyronine (144 before, 131 after 1 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:

This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all adverse or intended effects.

The patient (or parent/caregiver) should be instructed to seek medical advice whenever nausea, vomiting, persistent headache, insomnia, restlessness, or rapid heartbeat 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 informed that theophylline interacts with a wide variety of drugs (see **Table II**). They 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.

UNI-DUR Tablets *should not be chewed or crushed.* Information relating to taking UNI-DUR Tablets in relation to meals or fasting should be provided.

Drug Interactions

Drug/Drug Interactions:

Theophylline interacts with a wide variety of drugs. The interaction may be pharmacodynamic, ie, 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, ie, 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 (eg, 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 (eg, 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 listing of drugs in **Table II** is 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 be required to achieve desired effect.
Alcohol	A single large dose of alcohol (eg, 3 mL/kg of whiskey) decreases theophylline clearance for up to 24 hours.	30% increase
Allopurinol	Decreases theophylline clearance at allopurinol doses ≥600 mg/day.	25% increase
Aminoglutethimide	Increases theophylline clearance by induction of microsomal enzyme activity.	25% decrease
Carbamazepine	Similar to aminoglutethimide.	30% decrease
Cimetidine	Decreases theophylline clearance by inhibiting cytochrome P450 1A2.	70% increase
Ciprofloxacin	Similar to cimetidine.	40% increase
Clarithromycin	Similar to erythromycin.	25% increase
Diazepam	Benzodiazepines increase CNS concentrations of adenosine, a potent CNS depressant, while theophylline blocks adenosine receptors.	Larger diazepam doses may be required to produce desired level of sedation. Discontinuation of theophylline without reduction of diazepam dose may result in respiratory depression.
Disulfiram	Decreases theophylline clearance by inhibiting hydroxylation 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 theophylline clearance by inhibiting cytochrome P450 3A3.	35% increase. Erythromycin steady-state serum concentrations decrease by a similar amount.
Estrogen	Estrogen-containing oral contraceptives decrease theophylline clearance in a dose-dependent fashion. The effect of progesterone on theophylline clearance is unknown.	30% increase
Flurazepam	Similar to diazepam.	Similar to diazepam.
Fluvoxamine	Similar to cimetidine.	Similar to cimetidine.
Halothane	Halothane sensitizes the myocardium to catecholamines; theophylline increases release of endogenous catecholamines.	Increased risk of ventricular arrhythmias.
Interferon, human recombinant alpha-A	Decreases theophylline clearance.	100% increase
Isoproterenol (IV)	Increases theophylline clearance.	20% decrease
Ketamine	Pharmacologic.	May lower theophylline seizure threshold.
Lithium	Theophylline increases renal lithium clearance.	Lithium dose required to achieve a therapeutic serum concentration increased 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 greater effect.
Mexiletine	Similar to disulfiram.	80% increase
Midazolam	Similar to diazepam.	Similar to diazepam.
Moricizine	Increases theophylline clearance.	25% decrease

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBERS:

89-822 & 89-823/ S-001; S-002; S-004; S-005; S-008

BIOEQUIVALENCE REVIEW(S)

APR 27 1995

Theophylline (Uni-Dur)
Extended Release Tablets, 600 mg
ANDA #89-822/23
Reviewer: Gur J.P. Singh
File #89822SD.395.

Schering-Plough
Kenilworh, NJ 070803
Submission Dates:
March 20, 1995

Review of dissolution data and a multiple-dose bioequivalence study

Background

Schering-Plough's theophylline 600 mg extended release (ER) tablet (Uni-Dur) was given approval on January 4, 1995. In the approval letter, the sponsor was advised of interim dissolution specifications given below, and it was stated that the final specifications would be established upon review of dissolution data for three production lots.

Recommended interim dissolution specifications:

Time (hr)	Dissolution Range (%)
1	[redacted]
8	[redacted]
12	[redacted]
16	[redacted]
24	NLT [redacted]

These interim specifications were based on the following dissolution data submitted in the ANDA #89-822/823:

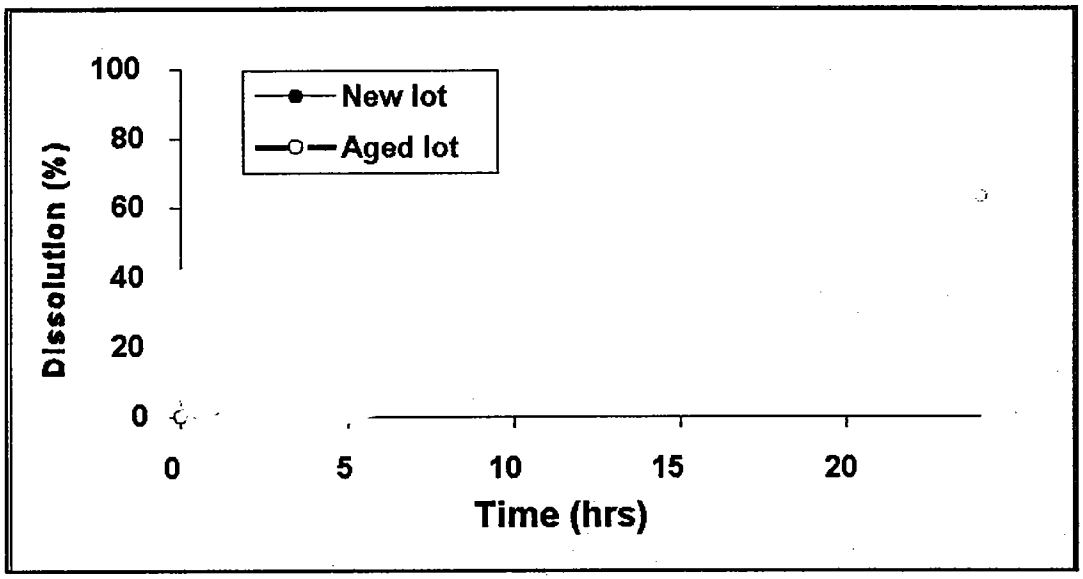
	Lot # B-110-021BB		Lot #91005-000-01	
Time (hr)	Mean (%)	Range (%)	Mean (%)	Range
1	10	[redacted]	10	[redacted]
8	32	[redacted]	32	[redacted]
12	44	[redacted]	45	[redacted]
16	59	[redacted]	58	[redacted]
24	85	[redacted]	85	[redacted]

The interim dissolution specifications recommended by the Division of bioequivalence were based on the *in vitro* dissolution data for two lots which underwent bioequivalence

evaluation. The dissolution windows recommended for various time points were wide enough to accommodate minor differences between production lots.

On January 11, 1995, the firm submitted the following dissolution data on a newly manufactured and an aged lot of Uni-Dur 600 mg tablets.

	New Lot (# 22764-20F-1)		Aged Lot (#-104-091A-2)	
Time (hr)	Mean (%)	Range (%)	Mean (%)	Range (%)
1	9	[redacted]	9	[redacted]
8	31	[redacted]	30	[redacted]
12	44	[redacted]	40	[redacted]
16	60	[redacted]	49	[redacted]
24	82	[redacted]	63	[redacted]



Based on the dissolution data for the aged lot, the sponsor felt that the interim specifications for dissolution of Uni-Dur 600 mg tablets at 12, 16 and 24 hours time points were too tight. Therefore, the firm requested that the dissolution specifications be revised to accommodate the following proposed specifications:

APPEARS THIS WAY
ON ORIGINAL

Time (hr)	Dissolution Range (%)
1	—
8	—
12	—
16	—
24	NLT —

The basis for sponsor's request for widening the dissolution specifications for the 12, 16 and 24 hours time points is the dissolution profiles of new and aged lots of Uni-Dur which do not meet agency's interim specifications (see Table 1, attachment). The Division of Bioequivalence is concerned with the *in vivo* performance of Uni-Dur 600 mg production lots considerably differing in their *in vitro* release profiles from those lots which underwent bioequivalence evaluation. This is because with theophylline controlled release products dissolution is a step limiting phenomenon; deviations in dissolution profiles may significantly affect the *in vivo* performance of drug these products.

To address these concerns, the sponsor has submitted (March 20, 1995) a bioequivalence study on the above mentioned new and aged lots of Uni-Dur 600 mg tablets. The firm feels that the results of this study support widening dissolution specifications as requested. The sponsor states that the dissolution specifications should be based on the results of *in vivo* multiple dose studies, instead of the single dose studies, because Uni-Dur is an extended release formulation designed for once daily administration. The sponsor suggests that prior to attainment of steady-state conditions, individual subject differences in absorption and excretion which influence the variation associated with plasma theophylline concentrations are not related to characteristics of the dosage formulation. Furthermore, the Agency has previously permitted the use of multiple dose study data for bioequivalence documentation when a single dose study failed to prove bioequivalence. The sponsor refers to the July 12, 1992 conference call between Schering representatives and the Division of Bioequivalence regarding the use of a multiple dose study to support a manufacturing site change (Miami Florida vs Las Piedras, Puerto Rico), when a single dose study was found to be unacceptable. It states that during this conversation, "FDA agreed with Schering's proposal to utilize a multiple-dose design for *future studies*", as of July, 1992.

In addition to the multiple dose study, the sponsor also submitted the dissolution data for twenty four (24) stability batches which represent 12 production lots. Of these eleven (11) lots were made up of Uni-Dur 600 mg tablets, and the remaining one lot contained Uni-Dur 400 mg tablets.

Dissolution Data:

Dissolution data submitted on March 20, 1995 are summarized, in table 1 (attachment), with respect to the interim specification recommended by the Division of Bioequivalence. The sponsor has provided data for mean and range of dissolution; individual tablet data were not submitted. Furthermore, it was not clear if dissolution test employed six or 12 tablets. Nonetheless, the reviewer has examined this data set to determine if the dissolution testing meets Agency specifications based on six tablets, because previous dissolution testing on stability batches of Uni-Dur 600 mg tablets employed 6 tablets.

Dissolution data submitted on March 20, 1995, can be divided into two categories; (A) initial testing of a newly manufactured lots and (B) dissolution during stability testing ranging from 3-24 months. Based on the range of dissolution during initial testing, 5 out of 24 batches failed to meet agency's dissolution specification for 12- and 24-hour time points.

Of the twenty 22 batches of Uni-Dur 600 mg tablets, 21 batches failed to meet dissolution testing at one or the other time points (see table 1, attachment). All these 21 batches failed to meet the interim dissolution specification of "NLT —— for the 24 hour time point. The 400 mg tablets met dissolution specifications.

The reviewer also examined dissolution data for 20 stability batches of Uni-Dur 600 mg tablets submitted on October 18, 1990. Among these, 13 batches failed to meet Agency specifications (see Table 2, attachment).

IN VIVO BIOSTUDIES

Screening Study

Prior to initiation of the multiple dose study discussed below, each subject participating in this study was screened for theophylline elimination half life and total body clearance. During this screening phase, a single 500 mg dose of an immediate release theophylline formulation (Slo-Phyllin tablets, 100 mg, William H. Rorer) was administered to each of the 30 participating subjects following an overnight fast. Blood samples (7 mL each) were collected at 0 (predose), 1, 2,4, 6, 8,15 and 25 hours after the dose. The results of the screening study are given on pages 89-164. Theophylline total body clearance and its elimination half life data are attached herewith. Of the 30 subjects participating in the screening study, 20 subjects were enrolled for the bioequivalence study. Theophylline total body clearance of these 20 subjects was in the range of 2.39 to 5.42 $L.hr^{-1}$, and its elimination half life was in the range of 4.64 to 11.0 hours.

Multiple-dose bioequivalence Study

OBJECTIVE: To compare the multiple dose pharmacokinetics of theophylline from two lots of Uni-Dur 600 mg tablets with different dissolution profiles in a two sequence two-way crossover study. The reference lot (Lot # 22764-20F-1) was a newly manufactured lot, and the test lot (Lot #B-104-091A-2) was an approximately two years old lot. Dissolution profiles of these lots are given above.

STUDY SITE, DATES AND INVESTIGATORS:

Clinical Laboratory:
Principal Investigator:

Analytical Laboratory:

Analytical Director:

Protocol and Informed consent: Protocol (#15 used) and Informed consent for this study were approved by the Institutional Review Board of Peninsular Testing Corporation (7 members, pp 45)

SUBJECTS: Twenty (20) subjects participated in the multiple dose study. The age and weight of these volunteers were in the range of 19-35 years and 151-204 pounds, respectively. The subjects were accepted based on total body clearance levels (based on the screening study) and acceptable medical history as judged by physical examination, EKG and normal blood and urine laboratory tests . Subjects were not enrolled for this study if they had participated in another clinical study within four weeks prior to the study start. In addition subjects were excluded from this study based on the following criteria:

* A history of cardiovascular, neurological, gastrointestinal, hepatic, renal, hematological and/or respiratory disease.
* Abnormal laboratory test value(s) in the pre-study examination.
* Inability to understand the informed consent form.
* Participation in blood donation programs within 60 days prior to the study start.
* Subjects with other abnormal conditions that might affect pharmacokinetics of drugs.
* Known sensitivity to theophylline or related drugs.
* Institutional confinement.
* History or presence of alcohol or drug abuse.

STUDY DESIGN: The multiple dose study was conducted as two treatment, two sequence two-way crossover evaluation with the following subject randomization:

TREATMENT SEQUENCE		SUBJECT NUMBER
Phase I	*Phase II*	
A	B	1,3,4,7,10,11,12,15,16,19
B	A	2,5,6,8,9,13,14,17,18,20

(These subject numbers are different from those used for the pre-screen study)

where:

A = Uni-Dur 1 x 600 mg tablet, New lot #22764-20F-1, Lot size: [redacted] tablets, expiry date not given, administered once daily at 8 A.M. for five consecutive days.

B = Uni-Dur 600 mg tablets, Aged lot #B-104-091A-2, lot size: [redacted] tablets (manufactured from a production scale [redacted], expiry date not given, administered once daily at 8 A.M. for five consecutive days.

DOSING AND MEALS: Both treatments were administered at 8 A.M. with 180 mL of water for a total of five doses (over five consecutive days). No washout was allowed between two periods because of the multiple dose study design. A standard breakfast was served to all subjects at 7 A.M., lunch at 12:30 A.M. and dinner at 7 P.M. Xanthine containing food or beverages were not allowed during the study.

SAMPLE COLLECTION AND STORAGE: Blood samples (7 mL each) were collected by venipuncture using nonheparinized polypropylene tubes at 0 (predose) before the 3rd, 4th and 5th dose and then at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 24 hours following the 5th dose.
Blood samples were centrifuged within one hour and serum separated. Serum samples were stored at -20°C pending further analysis.

PHARMACOKINETIC DATA ANALYSIS: The steady state area under theophylline plasma concentration (AUCss) for 0-24 hours after the 5th dose was computed using the trapezoidal method. In addition, Cmax, Cmin and percent fluctuation were determined using serum theophylline concentrations. Cmin data for days 3,4, and 5 were used to determine the attainment of steady state. Percent fluctuation was calculated as {[(Cmax-Cmin)/Cavg]*100}.

All statistical analyses were performed using SAS package on VAX 8000 series computer. Analysis of variance (ANOVA) was performed on AUCss and Cmax. The 90% confidence intervals for AUCss and Cmax data were calculated using the untransformed data and employing two one-sided t-test procedure. However the reviewer has performed the ANOVA using the individual subjects AUCss and Cmax data submitted by the sponsor and

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PHARMACOKINETIC PROFILE:

Individual subject graphs of steady state theophylline concentrations (pp 309 -328) demonstrate similar steady state profiles after administration of the new and aged lots of Uni-Dur 600 mg tablets, with the exception of subject #10, 17 and 20. Of these three subjects, graphs for subjects #17 and 20 indicate lower fluctuations (over a period of 24 hours) in profiles of the aged lot, compared with those of the new lot.

Mean plasma concentration data for the test and the reference products are given in Table 3. At various postdose intervals, theophylline plasma concentration following administration of the aged lot were within 10% of that of the new lot. The Cmin for days 3, 4, 5 are indicative of attainment of steady state. The reviewer has also statistically verified the status of steady state.

A summary of theophylline pharmacokinetic parameters is also given in table 3. The aged lot had a mean AUCss of 176.5 $\mu g/mL.hr^{-1}$ and mean Cmax of 9.5 $\mu g/mL$ which were 1% and 4% lower than the respective values for the new lot.

Based on reviewer's calculations, the 90% confidence intervals for the untransformed and log-transformed AUCss, and Cmax data were in the acceptable range of 80-125% (see table 3, attachment). Statistical analyses of data for these parameters revealed no sequence or period effects.

Data regarding the aged/new lot ratios of AUCss and Cmax are given in Table 4. Based on either the ratio-of-means (table 3) or mean-of-ratios (t\Table 4), the difference in the bioavailabilty of the new and aged lot of Uni-Dur 600 mg tablets remains the same.

Comments

1. The sponsor has submitted dissolution data for 22 batches of Uni-Dur 600 mg tablets. Of these, 5 newly manufactured batches failed to meet the interim dissolution specifications. However during 3-24 months of stability testing, 21 batches failed to meet the Agency specifications including the requirement of NLT ~~—~~ at 24 hours of the dissolution testing. The reviewer also examined the dissolution data on 20 stability batches of Uni-Dur 600 mg tablets submitted on October 18, 1990. Among these, 13 batches failed to meet Agency's interim dissolution specifications.

2. As mentioned above the sponsor has requested for widening of dissolution specifications for Uni-Dur 600 mg tablets. To support its request, the sponsor has submitted a multiple dose bioequivalence study on a new and an aged lot which differ in dissolution rates at 12, 16 and 24 hours of dissolution testing. The results of this study indicate that, based on the steady state AUC_{0-24} and Cmax data, the aged lot is bioequivalent to the newly manufactured lot. These data suggest that the observed differences in the *in vitro* dissolution profiles may not compromise theophylline steady state bioavailability.

3. The Divsion of Bioequivalence has previosly expressed concern reagrding the use of multiple dose study data to support widening of dissolution specifications because there is a history of bioequivalence failures in single dose studies on Uni-Dur 600 mg tablets. Therefore the reviewer determined *in vitro-in vivo* correlation, if any, based on the single dose study data. The data used were from Uni-Dur studies previously submitted by the sponsor. Dissolution data and serum concentration profiles for two study data sets are given in Table 5 and 6. These data are indicative of *apparent* lack of correlation between the *in vitro* dissolution and *in vivo* serum concentration profiles of Uni-Dur 600 mg tablets.

   The *in vivo* data were used for Wagner-Nelson analysis to determine the fraction absorbed at various time points. The results of these analysis are given in Table 7. Data for percent theophylline absorbed was then compared with the *in vitro* dissolution data (Table 8). The results of this comparison show a good correlation (Type A) between *in vitro* dissolution and the fraction absorbed, and the correlation was strongest for dissolution between 0-8 hours.

The reviewer also examined the correlation (type C) between *in vitro* dissolution and serum theophylline levels. As shown in Table 9, the dissolution data for 0-24 hours did not exhibit strong correlation with theophylline serum concentrations. The analyses discussed above suggest that, though *in vitro* dissolution may be related to the fraction absorbed, the serum concentration profiles may differ significantly. These results also indicate that differences in serum concentration profiles of two lots of Uni-Dur 600 mg tablets may not reflect differences in their *in vitro* dissolution, and vice versa.

The results of the multiple dose study submitted in support of sponsor's request for widening dissolution specifications demonstrate good type-A and type-C*in vitro-in vivo* correlation. These results indicate that changes in the *in vitro* dissolution (within certain limits), may not compromise product bioequivalence because bioequivalence is based on pharmacokinetic parameters derived from serum/plasma theophylline concentrations. Therefore widening of dissolution specifications requested by the sponsor may be granted.

Recommendations

1. The *in vivo* multiple dose bioequivalence study conducted by Schering comparing an aged (#B-104-091A-2) and a newly manufactured (#22764-20F-1) lot of its Uni-Dur 600 mg tablets has been found to be acceptable to the Division of Bioequivalence. The results of this study demonstrate that the aged lot Uni-Dur tablet is bioequivalent to its newly manufactured lot despite considerable differences in dissolution profiles of these two lots.

2. The interim dissolution specifications for dissolution testing on Uni-Dur 600 mg tablets should be revised as follows:

Time (hr)	Dissolution Range (%)
1	—
8	—
12	—
16	—
24	NLT —

Gur Jai Pal Singh, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED RPatnaik
FT INITIALLED RPatnaik 4/27/95

CONCUR: Keith Chan, Ph.D. 4/27/95
Director
Division of Bioequivalence.

GJPSINGH/4-18-95/89822SD.395
CC: ANDA# 89-822/823 (Original, duplicate), HFD-630 (OGD), HFC-130 (Jallen), HFD-600 (Hare), HFD-655 (Patnaik, Singh), Drug File, Division File.

TABLE 1. Dissolution testing failures* to meet Agency specifications
ANDA #879822/23, Submission Date: March 20, 1995

			DISSOLUTION TESTING	
	Bulk Lot #	Package Lot #	INITIAL (New lot)	STABILITY (3-24 months)
	B-110-023AA	B-110-023A-12		+
		B-110-023A-11		+
**	B-110-021BB	B-110-021B-12		+
		B-110-021B-13	+	+
	07210253	B-112-026D		+
		B-112-026C	+	+
	07210252	B-112-026B		+
		B-112-026A	+	+
	07210251	B-112-025D		+
		B-112-025C		+
	07210250	B-112-025B		+
		B-112-025A		+
	07210246	B-112-023B		+
		B-112-025C	+	+
	07210245	B-112-022B		
	(400 MG)	B-112-022A		
	07210378	B-112-050B		
		B-112- 50A		+
	07210377	B-112-048B	+	+
		B-112-048A		+
	07210376	B-112-043B		+
		B-112-043A		+
	07210375	B-112-042B		+
		B-112-042A		+
TOTAL	12	24	5	21

** see Table 1A (attachment) for details*
*** Biostudy lot (513800 tablets)*

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TABLE 2. Dissolution testing failures to meet Agency specifications
ANDA #879822/23, Submission Date: October 18, 1990

		DISSOLUTION TESTING	
	Package Lot #	INITIAL (New lot)	STABILITY (3-24 months)
	P8137	+	+
	P8270		+
	B-104-089A	+	+
	B-104-089B	+	+
	B-104-089C	+	+
	B-104-090A	+	+
	B-104-090B	+	+
	B-104-090C	+	+
	B-104-091A		+
	B-104-091B		+
	B-104-091C		+
	B-105-89		+
	B-105-90		+
	B-106-020		
	B-106-013A		
	B-106-013B		
	B-106-013C		
	B-106-017		
	B-106-018		
	B-106-019		
Total	20	7	13

Table 3: Theophylline serum concentrations (mcg/mL) and steady state parameters following administration of newly manufactured and aged lots of Uni-Dur 600 mg tablets

Time (hr)	New Lot (A)		Aged Lot (B)		B/A	
	Conc	%CV	Conc	%CV		
Day-3, 0		34		42		
Day-4, 0		42		41		
Day 5, 0		36		36		
2		25		26		
4		20		21		
6		24		22		
8		27		27		
10		26		29		
12		31		33		
14		32		34		
16		34		37		
18		40		43		
20		44		44		
22		43		47		
24		41		46		
PARAMETERS						
						90% CI Log)*
AUCss (mcg/mL*hr)	177.6	27	176.5	30	0.99	91.08 - 108.02
Cmax (mcg/mL)						
Cmin (mcg/mL)						
CSS (mcg/mL)						
% Fluct. (Mean)	75.1 (54-142)	34	67.5 (49-121)	44	0.90	

** 90% CI values are based on reviewer's calculations using the log transformed data. The 90% CI values for the untransformed AUCss and Cmax data were and , respectively.*

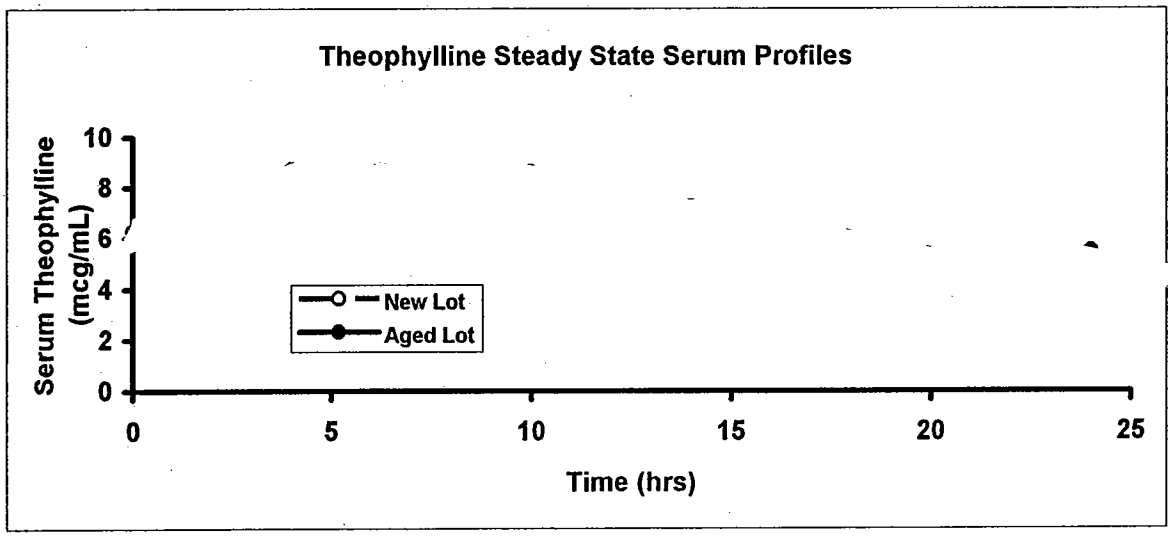

Table 4: Individual subject AUCss and Cmax data for study #89-401-01
(ANDA #89822/23)

	New Lot (A)		Aged Lot (B)		B/A	
SUBJECT #	AUCss	Cmax	AUCss	Cmax	AUCss	Cmax
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
Mean						
SD						
%CV						
Min						
Max						

APPEARS THIS WAY
ON ORIGINAL

3/20/95 dissolution data

Redacted 8

Page(s) of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBERS:

89-822 & 89-823/ S-001; S-002; S-004; S-005; S-008

MEDICAL OFFICER REVIEW(S)

S-004

PULMONARY MEDICAL OFFICER CONSULT

Label supplement to ANDA #:		**89-822, 89-823**
PRODUCT:		**Uni-Dur™**
CATEGORY OF DRUG:		**Sustained release theophylline**
SPONSOR:		**Schering-Plough**
DOSAGE FORM:		**400 mg, 600 mg sustained release tablet**
CONSULT BY:		**Mary E. Purucker, MD-PhD**
THROUGH:		**Robert J. Meyer, MD - Team Leader**
CONSULT TO:		**Larry Galvin, OGD**
PURPOSE OF CONSULT:		***Evaluate clinical/efficacy studies***
DATES:	**Submitted:**	**August 24, 1995**
	Received for consult:	**December 5, 1995**
	Reviewed:	**February 26, 1996**
	Consult date:	**March 6, 1996**

Introduction:

Theophylline is a bronchodilator which is used extensively in the management of reversible airways obstruction. It is available as extended release oral formulations which can be dosed less frequently, thereby providing convenience to the patient and potentially improving patient compliance. Uni-Dur™ is one such product which is currently approved for once daily dosing, given in the morning. This labeling supplement to ANDA 89,822 (Uni-Dur 400mg) and ANDA 89,823 (Uni-Dur 600 mg) is submitted for a labeling change that permits dosing once daily in the evening. The Division of Pulmonary Drug Products has been consulted to review the clinical trials submitted to support this labeling change.

Materials Submitted:

This submission consists of 20 volumes 2.1 through 2.20. The clinical trials contained therein consist of two controlled and three uncontrolled clinical studies in patients with reversible airway obstruction, predominantly patients with asthma, who were switched from a twice daily theophylline product to Uni-Dur QD, dosed in the evening.

Format of Consult:

This consult will consist of 2 parts. The first part is the consultative conclusions based upon our review. The second part is the actual review of the clinical studies - primarily the controlled studies S87-056 and I88-201. Because these two pivotal studies are the controlled and therefore more relevant studies from the regulatory standpoint, their review forms the basis for our conclusions regarding the safety and efficacy of Uni-Dur for the proposed indication. The results of the three uncontrolled studies, though reviewed, will not be explicitly discussed.

Within the text of our review section, *Reviewer's Comments* are included in

italics to provide commentary on those elements of the submission we feel are of particular significance to the overall review and conclusions.

PART 1

Consultative Conclusions:

The controlled studies, S87-056and I88-201, do not support the label claims regarding the safety and efficacy of Uni-Dur dosed in the evening relative to Theo-Dur dosed twice daily at the same total daily dose.

From the efficacy standpoint, these studies are seriously flawed in their design and conduct. Because of these flaws, they are not interpretable for efficacy. The studies were designed to be positive-control equivalence trials, with no placebo comparator and inadequate blinding given the subjective endpoints. The lack of a placebo group in an equivalence trial results in there being no way to assess the sensitivity or success of these trials for identifying any clinically significant differences in efficacy between Uni-Dur and Theo-Dur, should such a difference in fact exist. It is quite plausible, for instance, that given the modest bronchodilatory effects of theophylline, placebo would not have been distinguished as "significantly different" from the active treatments on many of the sponsor's 'endpoints of interest.' If that were the case in these trials, which we cannot exclude, the finding of no difference between the two active controls could not be taken as any kind of reassurance of clinical comparability. Secondly, although equivalence trials, these studies were powered as if they were superiority trials, meaning that they were very much underpowered, since the important error becomes the β error. Therefore, these trials by chance alone would have been expected to fail to detect any true differences over 20% of the time. Given all this, the sponsor appears to equate *failing to reject the null hypothesis* of there being no difference between the efficacy of an evening daily dose of Uni-Dur and twice-daily Theo-Dur as being the same scientifically as *accepting this null hypothesis.* This is clearly erroneous. In fact, for many of the efficacy endpoints, it appears that Uni-Dur was numerically inferior to Theo-Dur, though not statistically so. Without knowing over-all effect size, the clinical importance of this numerical inferiority cannot be judged. Another major deficiency in these studies was the failure to address maintenance of efficacy by spirometric parameters at the end-of-dosing interval. All such PFT measures were taken at predicted peak serum levels, which is a less informative time point for comparatively examining a BID vs. a QD regimen. For all these stated reasons, we do not feel that these data can be considered to support the sponsor's claims on page 9 of their draft labeling that *"Uni-Dur administered once-a-day in the evening has been shown to maintain pulmonary function similar to theophylline twice a day."* We would add, however, that with the use of the word *'similar'* and with the statement made only with regard to

pulmonary function, the efficacy data from these trials do not directly refute this statement either.

From the Safety standpoint, Uni-Dur dosed once-daily in the evening proved to be clearly less well tolerated in these trials than Theo-Dur BID, to a statistically significant degree in study S87-056. Though these resultant adverse events did not appear to be often times severe nor serious in nature, they were clearly indicative that patients did not tolerate this switch in therapy as well as the sponsor claims in the label. We strongly disagree with the sponsor's claim in the draft labeling from the same section as cited above that *"Uni-Dur administered once-a-day in the evening has been shown to maintain pulmonary function similar to theophylline twice a day with no increase in the incidence of adverse events."*

Since it appears that the serum theophylline AUC for Uni-Dur dosed in the evening is nearly identical to Uni-Dur dosed in the morning, and since the latter is an approved dosing regimen, we cannot state from the clinical standpoint that the claim for an evening dose should be disallowed. However, the clinical data that the sponsor submitted in support of such a change in the DOSAGE AND ADMINISTRATION section of the label does not support that claim relative to Theo-Dur, dosed BID. The proposed revisions to the CLINICAL PHARMACOLOGY section in reference to the clinical trials data appear even less substantiated by these clinical data. In fact, these data appear to directly refute the statement proposed by the sponsor with regard to comparable safety. It should also be noted that following the proposed labeling and substituting the Uni-Dur at the same total daily dose resulted in a higher number of subjects in both studies with theophylline levels significantly out-of-range. Therefore, any patients dosed in this manner would need careful follow-up with serum level monitoring to assure that theophylline toxicity is avoided.

PART 2

Study No. S87-056

Objective: "To evaluate the effects on patient comfort of conversion from twice-daily treatment with Theo-Dur to once-daily treatment with Uni-Dur dosed in the evening." [To evaluate the effects on patient preference of changing dosage forms, from Theo-Dur BID to 24-Hour Theophylline Sustained Release Tablet in patients with reversible airway obstruction.].

Reviewer's Comment: The objective as stated in the Protocol submitted as part of the General Study Documents (Appendix A-1, Volume 4) appears in [brackets]. Note that it differs from the objective as declared by the sponsor in the "Introduction and Objective" section of this submission. Supporting the single evening dose label change was not presumably an original objective of this Uni-Dur trial.

Design: This is a single blind (investigator), randomized, parallel group study comparing the clinical effects in each treatment group after randomization to those during the two week, open-label Theo-Dur period prior to randomization.

Summary of Protocol:

Patient Population

Inclusions:

- Adult, age > 12, male or nonpregnant, non-nursing female.
- Moderate or severe asthma, bronchitis, emphysema, $FEV_1 > 20\%$ of predicted.
- Reversibility of $FEV_1 \geq 15\%$ after Proventil inhalation.
- Theophylline use for at least the antecedent month.

Exclusions:

- Other medically significant disease.
- Use of cimetidine, troleandomycin, erythromycin, or a quinolone.

Reviewer's Comment: Current cigarette smoking was not prohibited, although it was recorded under patient demographics. This could have posed a problem if the randomization did not result in a comparable distribution of smokers into each group (since there was no stratification for smoking), and also if a change in smoking habits occurred disproportionately in the patients enrolled in one arm of the study versus the other. As illustrated once again by this PK study presented in this submission, smoking has a profound effect on STL. However, as the study turned out, there was only one reported smoker, in the Theo-Dur group. Urine cotinine levels were not done to detect unreported smoking.

Treatment arms: Stabilized on Theo-Dur BID for at least two weeks, then:

- Theo-Dur BID at same dose for two additional weeks beyond stability.
- Uni-Dur QD PM at same total daily dose as the previous Theo-Dur for two additional weeks beyond stability.

Blinding: The evaluating physician was blinded to patient treatment. However, patients were not blinded because, according to the sponsor, one of the primary endpoints was patient acceptance of the dosing regimen.

Reviewer's Comment: This poses a significant problem because one of the primary efficacy variables is patient evaluation of over-all drug effectiveness, a highly subjective endpoint which may therefore be biased in its results.

Sequence: This is a parallel study with a lead-in period of at least two weeks followed by a two week randomized period.

Assessments: During the lead-in, patients were assessed for STL every 3 days as needed to achieve a therapeutic level between 10 and 20 mcg/ml. When a therapeutic and well tolerated level was achieved, patients continued at that dose for an additional two weeks. They were assessed at baseline by routine history, physical exam, screening laboratory evaluation, ECG, spirometry (including FEV_1 and PEFR), and STL. They were given a diary for daily ongoing

personal assessments and were instructed to record PEFR twice daily, along with the times of theophylline doses, times of meals, any respiratory symptoms, usual concomitant bronchodilators, any additional bronchodilator use for increased respiratory symptoms, night wakenings due to respiratory symptoms, and any adverse events. Spirometry, STLs, and diaries were reviewed again at the time of randomization and again once therapeutic STLs had been achieved on the assigned protocol medication. These spirometry studies were performed at the presumed C_{max} of each of the study drugs.

Reviewer's Comment: Of interest, the C_{max} for Uni-Dur was measured at approximately 12 hours when dosed in the evening versus 8 hours for Uni-Dur dosed in the morning, according the pharmacokinetics study K87-009-01.

All assessments performed at baseline were also performed at the final study visit, two weeks following randomization or at study withdrawal. During the final visit, the patient was asked to compare his or her respiratory status overall during the two weeks of randomized treatment with the status as he or she recalled it during the lead-in treatment with Theo-Dur BID. The evaluating physician was also to assess the patient's response to therapy in the same manner. All personnel involved in efficacy evaluations were to be unaware of the test drug and dose being taken and of serum theophylline level. Conversely, personnel involved with the test drug dosing and serum theophylline levels were not to be involved in any efficacy evaluations.

Reviewer Comment: Although the sponsor states that the reasons that the subjects were not blinded is because the trial was to assess patient preference of treatment, it appears that the question asked was aimed specifically at whether the subjects felt their lung disease was controlled, as opposed to global questions regarding patient preference of ease and tolerance of dosing. Since this is the case, their case for making this a single-blind trial appears to be unfounded.

Concurrent Medications: Patients could continue their pre-study corticosteroids, cromolyn and anticholinergics provided the dosages remained unchanged. Medications resulting in exclusion from or discontinuation from participation in the study included cimetidine, troleoandomycin, erythromycin, quinolone antibiotics, any hypertensive medication other than a diuretic, burst therapy with corticosteroids required for asthma exacerbation, and any other medication indicating the presence of a significant underlying medical condition. Several other medications were excluded on a case-by-case basis.

Reviewer's Comment: One patient enrolled in the Uni-Dur arm had to be excluded for a toxic theophylline level of 34 mcg/ml following therapy with the H_2-blocker famotidine. Patients taking other H_2-blockers such as ranitidine were not excluded. (The sponsor may later have perceived this as a problem because an amendment to study No. I88-201, conducted after this current study, defines ranitidine as an excluded concomitant medication).

Exclusion criteria based upon chronic medication usage seemed to be arbitrarily

applied. For example, one patient taking captopril for hypertension was excluded while another patient using verapamil for the same indication was not (both of these agents can potentially impact on asthma control and may have confounded the study data). In addition, patients with chronic GI disturbances which could potentially affect theophylline absorption were not excluded: one patient with ulcerative colitis and chronically receiving Pancrease completed the trial and were included in the analysis. A further troubling trial design issue was the failure to account for patients begun on antibiotics during the trial, especially for respiratory/URI symptoms, since this could again be a source of confounding (see below).

Compliance: Compliance was assessed by review of patients' diaries and by STLs by an unblinded physician or observer.

Patient Withdrawal: Of the 149 patients screened for the study, 137 were accepted for the lead-in, 124 completed it and were randomized to study medication. Of the 124 randomized patients, 7 withdrew because of adverse experiences, 4 in the Theo-Dur group and 3 in the Uni-Dur group. None of the adverse experiences were reported as serious.

Endpoints:

Efficacy: The primary and secondary efficacy endpoints were to be measured during the randomized period and compared to the two week stable dosed lead-in period.

Primary Endpoints (Sponsor calls these 'Endpoints of Interest'):

- Patient evaluation of respiratory comfort*
- Respiratory symptoms**
- Quality of sleep*
- Physician evaluation of patient respiratory status*
- Number of nighttime awakenings for dyspnea.
- Number of actuations of extra bronchodilator.
- Morning and evening predose PEFR.
- FEV_1 taken at presumed peak STL.

* Rated on a three point scale, where 1 = good, 2 = fair, 3 = poor.

**Presence of dyspnea, wheezing, coughing, or chest tightness rated as 0 = absent, 1 = mild, 2 = moderate, 3 = severe.

Reviewer's Comment: It would have been useful to see the FEV_1 measured immediately prior to the next dosing interval for Uni-Dur, as this would better reflect the end-of-dosing interval effect. Measures of spirometry at peak serum levels is not very informative for testing the difference between two formulations of the same drug meant to be given at differing dosing intervals. Fortunately, patients were instructed to measure and record their PEFRs prior to dosing. Although not as standardized or reproducible as the FEV_1, these recordings provide some data relevant to the end-of-dosing efficacy.

In addition, the first three primary endpoints listed above are patient-based and

subjective. Because the study is not patient-blinded, the interpretation of any efficacy data from these endpoints is made very difficult, since they are greatly prone to bias.

Finally, the sponsor has declared eight 'endpoints of interest,' but it is not clear how disparate results were to be regarded. In other words, how would the sponsor have regard a significant disparity in one or two of these endpoints? This was never clarified prospectively.

Secondary Endpoints:

- Serum theophylline level (STL).
- Other spirometric measures such as FVC and MMEF.

Safety: Again, each safety assessment is to be compared between the randomized period and the two-week lead-in period.

- All adverse experiences.
- Change in screening laboratory values.
- Change in ECG.
- Serum theophylline level.

Statistical Analysis:

Patient evaluation and (blinded) physician evaluation of response was compared between the two treatment groups using the Wilcoxon test. Based on a sample size of 60 patients per group, it was calculated that there would be a 74% power to detect a treatment difference of 5% vs 20% failure rate (worse than open label phase based on physician evaluation) - i.e., a quadrupling of the rate at which physicians declared the therapy of interest as worse than the lead-in period, given an α level of 0.05.

Reviewer Comment: This is an equivalency trial, yet the sponsor is using a standard power analysis for a superiority trial. In an equivalency trial, the beta error is the crucial issue, and here the beta error was designed to be 26%, which is very large. Additionally, the sponsor's definition of clinically significant differences is very large. This study was only designed to detect a 400% increase in subjects that the investigators felt were inferiorly controlled during the randomized study period. These two features of the study design render this study very insensitive to detect any meaningful clinical or statistical differences in the obstructive airways disease control resulting from subjects being switched to Uni-Dur versus remaining on Theo-Dur. It is also important once again to remember that failure to reject the null hypothesis does not prove it to be true. In other words, the failure to demonstrate a significant difference between the Uni-Dur QD PM and Theo-Dur BID groups is not proof that they are equivalent.

Pulmonary function changes at each visit were calculated as percent change and change in percent predicted from the baseline evaluation. Those parameters, together with change in concomitant bronchodilators and number of night awakenings were analyzed via ANOVA for treatment, investigator and

treatment-by-investigator interactions.

Numbers of patients reporting adverse effects were compared between the two treatment groups using Fisher's Exact test.

Results:

Efficacy Analysis:

1. Patients' and Physicians' Evaluations: Patients were to rate disease control on a three point scale during the two week study period with the Theo-Dur BID lead-in. Blinded physician evaluators were also to evaluate the patients' disease control on this same scale. Overall, 88% of the Uni-Dur QD PM patients considered themselves the same or better compared to 95% of those randomized to continue Theo-Dur BID. If only subjects who considered themselves better controlled are considered, then there were 33% in the Uni-Dur group and 23% in the Theo-Dur. However, more of the Uni-Dur patients also rated themselves as worse, 12% vs. 5% for Theo-Dur. None of these findings were statistically significant. These impressions correlated with physicians' global evaluations, which found 90% of the Uni-Dur patients to be the same or better compared to 93% of the Theo-Dur patients, again not statistically significant. These numbers were similar to those found for the intent-to-treat population.

   Reviewer's Comment: There is a suggestion that both the investigators, who were apparently blinded, as well as the subjects rated the airways disease control on Uni-Dur to be more often inferior compared to the Theo-Dur.

2. Pulmonary Function Tests (FEV_1): FEV_1 was measured as baseline during the stabilized Theo-Dur lead-in phase and during the randomized period at predicted peak STLs. These values were expressed as mean change compared with the baseline, as well as the mean percent change in FEV_1. The results showed no significant differences between the two treatment arms. For percent change in FEV_1 from baseline to endpoint, the Uni-Dur group fell 2.51% (an absolute change of 0.10 Liters) vs. a fall of 0.13% in the Theo-Dur group (absolute fall of 0.02 Liters).

   Reviewer's Comment: Here in this objective endpoint, there does not seem to be an important difference in the PFTs measured at likely peak serum levels. (Note that the theophylline serum level data do support that at the times of the project peak, measured levels were as high or higher than all other periods for both Uni-Dur and Theo-Dur groups). However, although not statistically so, the patients on Uni-Dur were numerically worse at endpoint relative to the Theo-Dur subjects, compared to baseline. Also, a more important question than FEV_1 at peak serum levels is how the PFTs are maintained at the end of the dosing interval when going from a BID to QD preparation. Again, with the exception of the PEFR measured pre-dose in the evenings by the subjects, we are given no such data.

3. Patient Diary Entries: According to the sponsor, conversion to treatment with

Uni-Dur QD PM or continued treatment with Theo-Dur BID did not appear to affect quality of sleep or nighttime awakenings for dyspnea, the use of extra bronchodilator therapy during the day or the respiratory symptoms of shortness of breath, wheezing, and coughing. Interestingly, though not statistically different between the groups, nighttime awakenings scores fell from 0.39 to 0.28 in the Theo-Dur group, while they stayed stable in the Uni-Dur group (0.47 baseline to 0.48 at endpoint). Treatment of nighttime awakenings is one of the clinical reasons to prescribe a once-daily theophylline preparation in the evening. While PEFR measured by patients at approximately 8 AM and 8 PM was essentially unchanged in the Theo-Dur BID group between baseline and endpoint, mean PEFR values for the Uni-Dur QD PM group were somewhat higher at endpoint than at baseline (AM- 391.1 to 404.5 and PM-420.9 to 435.7). These mean changes from baseline to endpoint for both morning and evening PEFR values were significantly greater in the Uni-Dur QD PM group than in the Theo-Dur BID group ($p = 0.03$ and $p = 0.02$, respectively).

Reviewer's Comment: PEFR measured at 8 PM in the Uni-Dur group was to have been recorded by the patient prior to administering the next daily dose. It is important to note that Uni-Dur does not appear to have diminished or inferior efficacy at the end of its dosing interval as measured by PEFR, when compared to Theo-Dur at the end of its dosing interval.

4. Dose Adjustments and Serum Theophylline Levels: See *Safety Analysis*.

Safety Analysis:

1. Serum Theophylline Levels:

Seven of 60 (12%) Uni-Dur patients and 8/64 (13%) of Theo-Dur patients had STLs greater than 20 mcg/ml, defined by the sponsor as out-of-range. These values varied from [redacted] (median 25) with Uni-Dur, compared with [redacted] (median 22.5) with Theo-Dur:

Highest Theophylline Level	*Uni-Dur QD PM*	*Theo-Dur BID*
(mcg/ml)	*(# patients)*	*(# patients)*
[redacted]	*3*	*1*
	0	*3*
	0	*3*
	0	*1*
	1	*0*
	1	*0*
	1	*0*
	1	*0*

Reviewer's Comment: Although the overall number of subjects with potentially toxic theophylline levels appear the same between the groups, it should be

noted that the patients in the Uni-Dur group had more extreme elevations of their theophylline levels compared to those in the Theo-Dur group.

2. Adverse Experiences: During the open-label Theo-Dur lead-in period, 24% of the participants reported at least one adverse experience. Following randomization to blinded treatment, the incidence of adverse experiences in the Uni-Dur QD PM group was statistically significantly greater at 40% versus 23% with Theo-Dur BID. These were classified by the sponsor as predominantly "mild" or "moderate" and most commonly were reported as "caffeine-like" side effects: such as headache, nausea, or dyspepsia.

   Reviewer's Comment: The sponsor discounts the significance of this difference with regard to safety because the adverse effects were not serious and most of these effects could be attributed to the predictable actions of the methylxanthine class of drugs. However, these are precisely the side effects one might expect to elicit at higher serum levels of theophylline and should therefore be carefully considered, especially in subjects who were not otherwise theophylline naive at study entry.

3. Treatment Discontinuation because of Adverse Experiences: Despite the significant differences in overall adverse experiences, the dropout rate was not statistically different in the Uni-Dur group (2/60 [3%]) versus the Theo-Dur group (1/64 [2%]).

4. Laboratory, ECG, and Vital Sign changes: No significant changes in these parameters were reported pre- or post-treatment that suggest any clinically important difference in these parameters between the two treatments.

   Reviewer's Comment: Unfortunately, Vital Signs were only reported at the time of entry and not during the lead-in phase or at completion of the study.

Summary and Conclusions for study S87-056:

Efficacy Conclusions:

As measured by the sponsor's stated primary endpoints and analysis, this study is successful in demonstrating comparable efficacy between the two tested treatments. However, for all the reasons previously noted in this review, the sponsor's conclusion of comparable efficacy cannot be supported by this trial in our opinion. In fact, in many parameters, it appears that Theo-Dur during the study period was numerically superior to Uni-Dur. Although failure to obtain formal spirometry at the end-of-dosing interval is a significant design flaw as previously mentioned, the data arising from the patient measured pre-dose PEFRs were reassuring that efficacy measured at the end of the dosing interval for Uni-Dur was no worse, and in fact, was numerically better than that measured at the end of the Theo-Dur dosing interval.

Safety Conclusions:

The sponsor concludes that patients with reversible airway obstruction who have been maintained successfully on a 12-hour sustained-release theophylline product administered twice daily can safely convert directly to Uni-Dur

administered once daily in the evening at the same total daily dose. In fact, while there were few serious toxicities noted in this trial (the only potentially serious adverse event reported was a toxic STL of 34 mcg/ml which occurred in a patient in the Uni-Dur group in the setting of concomitant H_2-blocker therapy), significantly more of the Uni-Dur patients (40%) than the Theo-Dur patients (23%) complained of the adverse events. This 40% also exceeds that rate found in patients during the initial Theo-Dur lead-in period (24%). It is worth noting, though, that despite this impressive and statistically significant higher rate of adverse event reporting in the Uni-Dur group, discontinuations for adverse events were equivalent between the Theo-Dur BID and Uni-Dur QD PM groups, suggesting that these adverse events were tolerable. Also, it is worth noting that following the sponsors planned method for switching from BID to QD therapy, Uni-Dur patients tended to have higher resultant levels of serum theophylline when compared to those maintained on Theo-Dur, including the highest of the out-of-range levels.

These data do not, in our opinion, represent unacceptable toxicities. However, they imply that subjects who are switched to Uni-Dur from Theo-Dur dose for dose must have close follow-up, complete with serum levels, to assure that toxic levels/effects are not occurring or, if they occur, are promptly addressed. Further, these safety data, rather than supporting the sponsor's label claim of *'no increase in adverse events'* resulting from such a switch, appear to directly refute that claim.

Study No. I88-201

Objective: To evaluate the effects of changing dosage forms from Theo-Dur BID to Uni-Dur dosed once daily in the evening on pulmonary function in patients with reversible airway obstruction. [To evaluate the effects of changing dosage form from Theo-Dur BID to Uni-Dur QD PM on pulmonary function, patient preference, and physician evaluation].

Reviewer's Comment: Again, the objective as declared by the sponsor differs from that given in the Protocol submitted as part of the General Study Documents, which appears in [brackets]. The primary objective of this non-US study differs from the prior study in that spirometric parameters are the primary endpoints, rather than patient preference. Also, the baseline and treatment periods are 4 weeks in this trial. This change in primary endpoint and duration complicates any direct comparison of the two studies.

Design

This was a multicenter, randomized, repeated-dose open label parallel study comparing the effects of Uni-Dur administered QD PM with those of Theo-Dur administered BID, following approximately four weeks of lead-in treatment with Theo-Dur BID, in patients with reversible airway obstruction. Randomization was two-to-one, Uni-Dur:Theo-Dur.

Reviewer's Comment: This study did not apparently maintain any blinding, which again renders the subjective endpoints problematic for interpretation.

Summary of Protocol:

Patient Population

Inclusions: Identical to Study No. S87-056 except:

- $FEV_1 > 40\%$
- Over age 14 at study center I88-301-01.

Exclusions: Identical to Study No. S87-056 except:

- Interferon was added to the list of excluded medications.
- Ranitidine was added to the list of excluded medications.
- Allopurinol, influenza vaccine, or OCPs were excluded at study center I88-201-01.

Reviewer's Comment: With the exception of interferon, none of the above exclusions were present in the original protocol.

Treatment arms: Stabilized on Theo-Dur BID for at least *four* weeks, then:

- Theo-Dur BID at the same dose for *four* additional weeks.
- Uni-Dur QD PM at the same total daily dose for *four* additional weeks.

Blinding: This was an open-labeled trial, with no blinding.

Sequence: This was a parallel study with a four week lead-in followed by a four week randomized trial in a two-to-one ratio of total numbers of Uni-Dur patients to Theo-Dur patients.

Assessments: The overall scheme of assessment in this study was identical to the prior study, except that there was an interim assessment at the midpoint (2 weeks) of both the lead-in Theo-Dur period and randomized period.

Concurrent Medications: Patients could continue their pre-study corticosteroids, cromolyn and anticholinergics provided the dosages remained unchanged. Medications resulting in exclusion from or discontinuation from participation in the study were the same as the prior study except for ranitidine at all centers and allopurinol, influenza vaccine, and oral contraceptives at one center only.

Reviewer's Comment: Again, exclusion criteria appeared to be arbitrarily applied in this case. Some patients were continued in the study and included in the analysis even if they had an exacerbation requiring a steroid bolus during the lead-in (patients 1 and 14, center 201). Also, there were patients receiving ACE inhibiters or calcium channel blockers for hypertension, as well as anticonvulsants for seizure disorder who should have been excluded by entry criteria (patients 4, center 201 and 2, center 301). Finally, several patients received a course of antibiotics (including amphotericin B, patient 9, center 201) initiated and completed during the trial and were neither excluded nor accounted for in the analysis.

Endpoints:

Efficacy:

Primary Endpoints:

Again, comparisons were made between the Theo-Dur BID lead-in period to the randomized period on either Uni-Dur QD or Theo-Dur BID:

- PFTs performed at peak STL.
- Patient evaluation of respiratory comfort*
- Quality of sleep*
- Number of nighttime awakenings for dyspnea.
- Number of puffs of extra bronchodilator needed.
- Morning and evening PEFR.
- Respiratory symptoms**

  * Rated on a three point scale where 1 = good, 2 = fair, 3 = poor

  **Presence of dyspnea, wheezing, cough, chest tightness rated as 0 = absent, 1 = mild, 2 = moderate, 3 = severe

Secondary Endpoints:

- Serum theophylline level (STL)
- Number of dose adjustments

Safety:

- All adverse experiences
- Change in screening laboratory values.
- Change in ECG, compared to lead-in
- Serum theophylline level (STL) compared to lead-in

Statistical Analysis:

For the efficacy variables - FEV_1, FVC, FEF_{25-75}, and PEFR - statistical testing was performed on the mean change from baseline and mean change in percent predicted from baseline using an ANOVA with treatment, investigator and investigator-by-treatment interactions analyzed.

Patient symptoms, diary variables and STLs were compared between the two treatment groups using Wilcoxon's rank sum test. All the variables in the diary card daily scores were analyzed by ANOVA for by treatment, investigator and investigator-by-treatment interactions.

Wilcoxon's rank sum test was used to compare physicians' and patients' overall evaluation between the two treatment groups.

The number of patients reporting drug-related adverse effects were compared between the two treatment groups using Fisher's exact test.

With the sample size of 120 patients in a 2:1 ratio, the sponsor calculated that there would be an 80% power to detect a treatment difference of 5% vs 23% failure rate (i.e. randomized treatment is worse than baseline Theo-Dur BID based on physician evaluation) at the 0.05 level.

Reviewer's Comment: All previous comments of the problems related to

powering an equivalency trial and the problems with the sponsor's interpretation of failing to reject the null hypothesis of equivalence also apply to this trial.

Results:

Patient Withdrawal: Eighty-nine patients with reversible airway obstruction were enrolled and assigned Theo-Dur lead-in treatment. One immediately dropped out and yielded no information. Of the remaining 88 patients, 10 did not continue beyond the lead-in period and "were evaluable for safety only." Thus, 78 patients were randomized in a 2:1 ratio to receive Uni-Dur (53 patients) or Theo-Dur (25 patients). Of these 78, 7 patients were excluded from the efficacy analysis (6 Uni-Dur, 1 Theo-Dur) for the following reasons:

Treatment	Patient #	Center #	Reason
Theo-Dur	35	I88-201-01	Unacceptable baseline STL
Uni-Dur	17	201	Discontinued after 2 days because of adverse experience
Uni-Dur	15	310	Discontinued after 5 days because of adverse experience
Uni-Dur	22	201	Unacceptable concomitant therapy
Uni-Dur	8	301	Unacceptable concomitant therapy
Uni-Dur	17	301	Unacceptable concomitant therapy
Uni-Dur	23	310	Did not meet entrance criteria

This left 71 patients considered evaluable for efficacy by the sponsor, 47 on Uni-Dur and 24 on Theo-Dur. Of the 71 Uni-Dur patients, 3 switched over to Theo-Dur. Two switched because of adverse events while on Uni-Dur and each completed the study on Theo-Dur. The third patient was switched temporarily to Theo-Dur because of a low STL then switched back at a higher dose of Uni-Dur when a therapeutic level was obtained. All three patients were included in the safety analysis of the group to which they were assigned. Efficacy analysis was performed on valid visits while the patients were on Uni-Dur only.

Reviewer's Comment: The fact that there was an diproportionate imbalance in randomized subjects who had to be excluded from the efficacy analysis (6 Uni-Dur patients compared to only 1 Theo-Dur, while randomization was 2:1) is of concern. Patients who discontinue a particular therapy because of adverse experiences ought to be considered treatment failures, especially if the reasons for discontinuation relate directly to the medication. For example, patient 17 from center 201 discontinued because of headache, nausea, palpitations, and insomnia - typical theophylline toxicities. Unfortunately, no details of patient 15's adverse experience are provided in this submission. Patient 22 from center 201 had an asthma exacerbation on the same day as his switch to Uni-Dur and required bolus. This was unlikely to have been causally related to Uni-Dur, since it occurred so shortly after randomization. Patient 8 from center

301, on the other hand, was hospitalized for an asthma exacerbation 9 days into therapy with Uni-Dur and requiredsystemic steroids. Similarly, patient 17 from center 301 received a 50 mg bolus of prednisone on day 9 of therapy with Uni-Dur. In summary, 4 of the Uni-Dur patients excluded from the efficacy analysis should have been considered failures of therapy. If these four patients, as well as the two who switched from Uni-Dur to Theo-Dur for adverse events are factored into the efficacy analysis shown on page 35, Table 9 under "Overall Respiratory Status", 14 out of 51 or 27% of Uni-Dur patients would have been considered to be "worse" during the randomized treatment rather than 17%. This is compared to the 0% who were worse in the randomized phase on Theo-Dur. According to the statistical analysis outlined on page 64 of the Protocol under "General Study Documents", a difference of 18 in the percent failure rate was considered to be clinically significant by the sponsor. With these subjects factored in, it appears that this difference in worsening is clinically significant by the sponsor's own definition.

Efficacy Endpoints:

1. Pulmonary Function Tests: Pulmonary function tests - including FEV_1, FVC, FEF_{25-75}, and PEFR - were measured at predicted peak STL during the Theo-Dur lead-in (baseline) period and again following randomization to Uni-Dur or Theo-Dur at 1-6 days, 7-21 days, >21 days, and at the endpoint of the study. Mean values were obtained at each of these time points and the absolute value of the mean change, as well as mean percent change from baseline were reported for each of these two groups. These results do not show any clearly important trends or differences. This was true of both the efficacy and intent-to-treat population for the FEV_1. For instance, in the efficacy population analysis of FEV_1, the Uni-Dur group fell by -0.18% at endpoint, while the Theo-Dur group rose by 1.75% at endpoint. For the PEFR, the analysis of covariance of the intent-to-treat population showed a statistically significant difference ($p \leq 0.04$) in favor of the Theo-Dur BID group over Uni-Dur QD PM group for the >21 days and endpoint values.

   Reviewer's Comment: The spirometry data, being sponsor defined parameters of primary interest in this study, should be given the most weight in evaluating this study's support of the sponsor's efficacy claims for Uni-Dur. Unfortunately, these data are not well organized or presented and important values are often not reported. Reproducibility is an important question in judging the validity of these tests, since they have been measured by at least three different PFT labs. However, the reader is referred to tabulated data in Appendices C-4 to C-8 for "details" of mean and median values and statistical testing. Because each tabulated value is the average of several unpresented measures, it is difficult to verify the sponsor's statements independently, since the primary data are not given. A third problem with these data is the absence of planned spirometric testing at trough STL as a measure of efficacy at the end-of-dosing interval. The sponsor does provide "Bedtime (PM) PEFR" data as

part of patient diary entries in Appendix C-11, but does not specifically remark on it. Inspection of the data reveals that "Evening PEFR" was greater than "Awakening PEFR" for all time points for those patients randomized to the Uni-Dur arm, supporting no diminution in efficacy at the end-of-dosing interval.

Overall, despite the lack of statistical significance in most measures, it does appear that the Uni-Dur group is often numerically inferior to the Theo-Dur group when change in spirometry from baseline is considered.

2. Patients' and Physicians' Evaluations: As in the prior study, patients were to rate themselves as 'better,' the 'same' or 'worse' on study medication versus Theo-Dur BID during the lead-in. An unblinded physician evaluator was to use the same scale. Overall, 83% of Uni-Dur patients considered themselves unchanged or better compared to 100% of the Theo-Dur patients, not a statistically significant difference according to the sponsor. Similarly, the physician evaluator rated 87% of the Uni-Dur patients the same or better compared to 100% of the Theo-Dur patients, not statistically different.

   Reviewer's Comment: Conversely, 17% of the Uni-Dur patients considered themselves worse than before compared to none of the Theo-Dur patients, which by itself comes very close to meeting the difference that the sponsor defines as clinically significant. Further, as mentioned above, when the patients who withdrew due to treatment failure are added in, this percentage clearly exceeds the sponsor's own definition of a clinically significant decrease in efficacy. Similarly, the physician evaluators considered 13% of the Uni-Dur patients to be clinically worse compared to none of the Theo-Dur patients.

3. Patient Diary Entries: There were no significant differences between the randomized treatment groups in terms of sleep quality, number of nighttime awakenings for breathing discomfort, use of inhalational bronchodilator therapy, morning or evening PEFR as measured by the patients or by respiratory symptoms. However, in this study the nighttime awakenings score fell in the Uni-Dur group (from 0.57 to 0.50), but less so than the Theo-Dur group (0.65 to 0.50). The use of rescue beta agonist fell to a similar and rather minor degree over the treatment period in both arms of the study. Symptom scores for wheeze and cough numerically favored Uni-Dur, while in chest tightness they numerically favored Theo-Dur.

4. Serum Theophylline Levels: See *Below.*

Safety Analysis:

1. Serum Theophylline Levels: Supratherapeutic STLs were document on 11 occasions, once in a Theo-Dur patient (4%), and on 10 occasions (in 9 different patients) or 17% in the Uni-Dur group. The Theo-Dur patient did not experience any treatment-related adverse experience. On the other hand, seven of the nine Uni-Dur patients reported adverse experiences thought to be related to the study treatment. One adverse experience was rated as severe by the patient (headache) and another patient with a supratherapeutic STL discontinued

therapy as a result of an adverse experience. The other patients reported mild or moderate symptoms.

Reviewer's Comment: Of interest, the average daily dose of both the lead-in Theo-Dur and Uni-Dur was 800mg, as compared to 800 mg and 750 mg, respectively, in the prior study.

2. Adverse experiences: The sponsor reports "treatment-related" adverse experiences as 62% (33/53) for the Uni-Dur patients vs 24% (6/25) of the Theo-Dur patients during the study treatment period and 39% during the Theo-Dur lead-in period.

   Reviewer's Comment: An examination of Appendix D-2 shows that "all adverse experiences" regardless of imputed causality also display a disparity: 66% (35/53) for the Uni-Dur patients vs 32% (8/25) for the Theo-Dur patients. Again, these data appear to directly refute the proposed statement in the labeling that subjects can be transferred from BID preparations to Uni-Dur-Dur dosed Q pm with 'no increase' in adverse events.

3. Treatment Discontinuation Because of Adverse Experiences: According to the sponsor, fifteen patients discontinued this study due to "treatment-related" adverse experiences. Three discontinued prior to randomization, one patient discontinued after being randomized to Theo-Dur, and 11 patients discontinued after being randomized to Uni-Dur.

   Reviewer's Comment: Unfortunately, there is no formal reporting by the sponsor of treatment discontinuations because of <u>all</u> adverse experiences. Nevertheless, there is a higher incidence of adverse effects in the Uni-Dur group which seem to be attributable to the study medication. This translates into a high patient dropout rate, even when the 3 discontinuations during the lead-in phase are attributed to Theo-Dur (4 Theo-Dur vs. 11 Uni-Dur).

4. Laboratory, ECG, and VS changes: There were no clinically important changes in these parameters were reported pre- or post-treatment.

<u>Summary and Conclusions</u>:

<u>Efficacy Conclusions</u>: If dropouts are included in the efficacy analysis as treatment failures (i.e., "worse" overall respiratory status, see "Patient Withdrawal" above), then 24% of the Uni-Dur patients compared to 0% of the Theo-Dur BID patients considered themselves "worse" on randomized treatment. This exceeds the 18% difference in failure rate set forth by the sponsor as clinically significant. Furthermore, although the spirometric parameters do not show a statistical difference, most numerical trends favor Theo-Dur treatment. Although the differences are not large, it must be borne in mind that this study was not properly powered for detecting a meaningful difference (with a β-error computed from a large difference in failure rate). We therefore conclude that Uni-Dur cannot be considered equivalent in efficacy to the Theo-Dur BID comparator based on the findings of this study.

<u>Safety Conclusions:</u> 66% (35/53) of Uni-Dur patients reported adverse

experiences compared to 32% (8/25) of Theo-Dur patients. At least 7 of these 35 Uni-Dur patients (20%) had supratherapeutic STLs at the time of the experience and one of these discontinued therapy as a direct result of the adverse experience. Furthermore, 11 patients randomized to Uni-Dur discontinued treatment because of adverse experiences compared to one patient who discontinued for adverse experience after being randomized to Theo-Dur. We would argue that the significantly higher rate of adverse events, especially those directly connected to a potentially toxic STL or leading to patient discontinuation, directly refutes the sponsor's claim in the clinical pharmacology section of the proposed labeling that such a change from BID to QD dosing can be accomplished with no increase in adverse events.

Supportive Trials

Because we do not feel that the reviewed controlled trials support the proposed labeling claims, we will not comment further on the other non-controlled trials in the submission. These trials do not add any useful data to support the sponsor's label claims. What safety data is included do not support the conclusion of comparable tolerance of Uni-Dur dosed in the evening compared with BID dosing regimens.

Original Primary Review by:

Mary Purucker, MD-PhD
Medical Officer, Pulmonary Group

Secondary Review by:

Robert J. Meyer, MD 3/7/96
Medical Team Leader, DPDP

Signed for Dr. Purucker

3/12/96 Division Director 3/7/96

I concur with Drs Purucker & Meyer that the clinical studies do not support the labeling claims proposed by the sponsor. I, however, also agree that the QD dosing regimen may be approved based on pharmacokinetics (after formal review by DSD) with appropriate precautions in the labeling for Uni-Dur product 18 & serum follow up of patients.

cc: Div. File, HFD-570
HFD-570/Purucker/Medical Reviewer
HFD-570/Meyer/Team Leader
HFD-650/Ripper

LRipper
HFD-102
3/20/96

Division of Pulmonary Drug Products Consult - Addendum

Label supplement to ANDA #: 89-822, 89-823

PRODUCT: Uni-Dur

CATEGORY OF DRUG: Sustained release theophylline

SPONSOR: Schering-Plough

DOSAGE FORM: 400 mg, 600 mg sustained release tablet

CONSULT BY: Robert J. Meyer, MD - Team Leader

CONSULT TO: Carol Holquist, OGD

PURPOSE OF ADDENDUM: Revised Recommendations from 3-6-96 Consult

DATES: Original Consult Date: March 6, 1996

Addendum Consult Date: November 18, 1996

Overview:

The Division of Pulmonary Drug Products reviewed clinical studies submitted in support of P.M. dosing of Uni-Dur by Schering-Plough and made consultative recommendations to OGD in a consult dated 3-6-96. At the time of the 3-6-96 consult, the full background of the original approval and the approval of evening dosing for Uniphyl (Purdue-Frederick s sustained release theophylline which has been previously approved for once-a-day P.M. dosing) was not available to DPDP. The Office of Generic Drugs has requested that DPDP revisit our recommendations taking into account the precedent of the Uniphyl approval. OGD has provided to DPDP a packet of meeting notes, consult reviews and other materials related to the Uniphyl approval process. This Addendum consult represents DPDP s response to OGD s request after review of these materials. Also, this addendum consult takes into account the conclusion by OGD that the PK comparisons included in the Uni-Dur application support P.M. dosing and that the comparative safety profile from these PK comparison studies was satisfactory.

Recommendations:

Schering presented two main controlled studies, S87-056 and I88-201, in support of the P.M. dosing of Uni-Dur. While these studies alone would not be of sufficient quality to support the efficacy of once-a-day P.M. dosed Uni-Dur, when taken together with pharmacokinetics data, efficacy of Uni-Dur dosed in this fashion can be inferred. Further, it appears that the quality and quantity of these clinical efficacy data equals or even exceeds that which was available for the approval of P.M. dosing for Uniphyl. The latter approval was originally supported primarily by PK data, as well as a published clinical trial that appears to have been of similar quality to the clinical trials in this Uni-Dur application. At a later date, in response to an original restriction on P.M. dosing of no more than 800 mg, the sponsor of Uniphyl submitted a study of P.M. dosed versus A.M. dosed Uniphyl for safety and efficacy purposes. This study again was not of optimal design, but supportive

of comparability of the PK profile, safety and efficacy of the evening and daytime once-a-day regimen.

As for the safety data available in this application, while there were numerical differences in the safety profile of P.M. dosed Uni-Dur versus twice daily dosed Theo-Dur with an excess of caffeine-like ADRs for the P.M. dosing, these ADRs were not of sufficient magnitude or severity to warrant a Not Approvable recommendation. Further, the proposed labeling contains a caution that peak and trough serum theophylline levels produced by the once-daily dosing may vary from those produced by the previous product and/or regimen along with some further instructions on serum level monitoring. Further, OGD has reported to us that Dr. Fanning s review of the A.M. vs. P.M. dosing PK study showed no important differences in the safety profiles of the two regimens.

Therefore, the DPDP recommends the approval of P.M. dosing of Uni-Dur based on the full information available. As stated in the March 6, 1996 consult, we continue to believe that the claim by Schering-Plough which reads Uni-Dur administered once-a-day in the evening has been shown to maintain pulmonary function similar to theophylline twice a day with no increase in the incidence of adverse events is problematic. While the efficacy statement is arguably true, as it only claims similar effects on PFTs, the later statement on no increase in ADRs is not supported by the studies reviewed. We recommend that this whole sentence be struck from the clinical trials section. Further supporting this deletion is that the Uniphyl label does not carry any such claim, so removing this statement would be more consistent with precedence.

Addendum Review by:

Robert J. Meyer, MD
Medical Team Leader, DPDP

Concurrence:

John K. Jenkins, MD, FCCP
Director, DPDP

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBERS:

89-822 & 89-823/ S-001; S-002; S-004; S-005; S-008

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION/MEETING

I called Mark Mariani to inform him the firm sent in the same labeling for S-004 and S-005. S-005 should contain another drug interaction. He looked at what they had sent and agreed it was incorrect. He stated he would send the correct labeling in for S-005 and I explained he could reference this telephone conversation.

APPEARS THIS WAY
ON ORIGINAL

DATE
4/30/97

ANDA NUMBER

89-823/S-005
89-822/S-005

IND NUMBER

TELECON

INITIATED BY
_ APPLICANT/ SPONSOR
X FDA

MADE
X BY TELE.
_ IN PERSON

PRODUCT NAME
Theophylline 600 mg and 400 mg(Unidur)

FIRM NAME

Schering

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Mark Mariani
DRA

TELEPHONE NUMBER

908-298-5713

SIGNATURE

C. Halquist 4-30-97

E L E C T R O N I C M A I L M E S S A G E

sitivity: COMPANY CONFIDENTIAL

Date: 19-Nov-1996 07:32am EST
From: Robert Meyer
MEYERRO
Dept: HFD-570 PKLN 10B45
Tel No: 301-827-1050 FAX 301-827-1271

TO: Jerry Phillips (PHILLIPSJ)
TO: Carol Holquist (HOLQUISTC)

Subject: Uni-Dur Consult

Attached you will find a copy of our "revised" consult based on the review of all the precedent material from Uniphyl. The signed off copy should be arriving shortly, but I wanted to give you the jump on this by including it in the e-mail.

Let me know if you have any questions!!

Thanks,

Bob Meyer

P.S. Thank you for getting all those materials to us quickly.
Waiting for conversion of WPCORP document...

APPEARS THIS WAY
ON ORIGINAL

E L E C T R O N I C M A I L M E S S A G E

Date: 20-Mar-1996 07:38am EST
From: John Jenkins
JENKINSJ
Dept: HFD-570 PKLN 10B45
Tel No: 301-827-1050 FAX 301-827-1271

TO: Leah Ripper (RIPPER)

Subject: RE: ANDA 89-822/3, Uni-Dur

Leah

We included some comments in the review about the labeling, specifically claims that the sponsor had included in the labeling that were not supported by the clinical studies. These obviously will be removed should the supplement be approved based on PK. I think we would like to wait until OGD decides on the status of the PK study before we review any final labeling (I don't think there were any changes other than the clinical claims that we said were not supported and the inclusion of the PM dosing alternative).

John

Purdue Frederick—Cont.

RUG ABUSE AND DEPENDENCE

ug abuse and dependence have not been reported with TRILISATE preparations.

OVERDOSAGE

Death in adults has been reported following ingestion of doses of from 10 to 30 grams of salicylate; however, larger doses have been taken without resulting fatality.

Symptoms: Salicylate intoxication, known as salicylism, may occur with large doses or extended therapy. Common symptoms of salicylism include headache, dizziness, tinnitus, hearing impairment, confusion, drowsiness, sweating, vomiting, diarrhea, and hyperventilation. A more severe degree of salicylate intoxication can lead to CNS disturbances, alteration in electrolyte balance, respiratory and metabolic acidosis, hyperthermia, and dehydration.

Treatment: Reduction of further absorption of salicylate from the gastrointestinal tract can be achieved via emesis, gastric lavage, use of activated charcoal, or a combination of the above. Appropriate I.V. fluids should be administered to correct dehydration, electrolyte imbalance, and acidosis and to maintain adequate renal function. To accelerate salicylate excretion, forced diuresis with alkalinizing solution is recommended. In extreme cases, peritoneal dialysis or hemodialysis should be considered for effective salicylate removal.

DOSAGE AND ADMINISTRATION

ADULTS: In rheumatoid arthritis, osteoarthritis, the more severe arthritides, and acute painful shoulder, the recommended starting dosage is 1500 mg given b.i.d. Some patients may be treated with 3000 mg given once per day (h.s.) In the elderly patient, a daily dosage of 2250 mg given as 750 mg t.i.d. may be efficacious and well tolerated. Dosage should be adjusted in accordance with the patient's response. In patients with renal dysfunction, monitor salicylate levels and adjust dose accordingly.

For mild to moderate pain or for antipyresis, the usual dosage is 2000 mg to 3000 mg daily in divided doses (b.i.d.). Based on patient response or salicylate blood levels, dosage may be justed to achieve optimum therapeutic effect. Salicylate od levels should be in the range of 15 to 30 mg/100 ml for ti-inflammatory effect and 5 to 15 mg/100 ml for analgesia and antipyresis.

Each 500 mg tablet or teaspoonful is equivalent in salicylate content to 10 gr of aspirin; each 750 mg tablet, to 15 gr of aspirin; and each 1000 mg tablet, to 20 gr of aspirin.

If the physician prefers, the recommended daily dosage may be administered on a t.i.d. schedule.

As with other therapeutic agents, individual dosage adjustment is advisable, and a number of patients may require higher or lower dosages than those recommended. Certain patients require 2 to 3 weeks of therapy for optimal effect.

CHILDREN: Usual daily dose for children for anti-inflammatory or analgesic action:

TRILISATE 500 mg Tablets/Liquid and TRILISATE 750 mg and 1000 mg Tablets, 50 mg/kg/day.

Weight (kg)	Total daily dose
12–13	500 mg
14–17	750 mg
18–22	1000 mg
23–27	1250 mg
28–32	1500 mg
33–37	1750 mg

Total daily doses should be administered in divided doses (b.i.d.). Doses of TRILISATE preparations are calculated as the total daily dose of 50 mg/kg/day for children of 37 kg body weight or less and 2250 mg/day for heavier children. TRILISATE Liquid is available for greater convenience in treating younger patients and those adult patients unable to swallow a solid dosage form.

CAUTION

Federal law prohibits dispensing without a prescription.

HOW SUPPLIED

NDC 0034-0500-80: TRILISATE 500 mg Tablets (pale pink, scored) supplied in bottles of 100 tablets.

NDC 0034-0500-50: TRILISATE 500 mg Tablets (pale pink, scored) supplied in bottles of 500 tablets.

NDC 0034-0500-10: TRILISATE 500 mg Tablets (pale pink, scored) supplied in unit dose packaging with 10 tablets per card. Ten cards are packed in each carton; 10 cartons are acked in each shipper.

C 0034-0505-80: TRILISATE 750 mg Tablets (scored, hite, film-coated) in bottles of 100 tablets.

NDC 0034-0505-50: TRILISATE 750 mg Tablets (scored, white, film-coated) in bottles of 500 tablets.

NDC 0034-0505-10: TRILISATE 750 mg Tablets (scored, white, film-coated) supplied in unit dose packaging with 10 tablets per card. Ten cards are packed in each carton; 10 cartons are packed in each shipper.

NDC 0034-0510-60: TRILISATE 1000 mg Tablets (scored, red, film-coated) in bottles of 60 tablets.

NDC 0034-0510-80: TRILISATE 1000 mg Tablets (scored, red, film-coated) in bottles of 100 tablets.

NDC 0034-0520-80: TRILISATE Liquid in bottles of 8 fl. oz. (237 ml).

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

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The Purdue Frederick Company, Norwalk, CT 06850-3590

U.S. Patent Number 4067974

July 24, 1991 Q145

Shown in Product Identification Section, page 323

UNIPHYL® Tablets ℞

[*ū'nĭ-fĭl*]

(theophylline)

400 mg

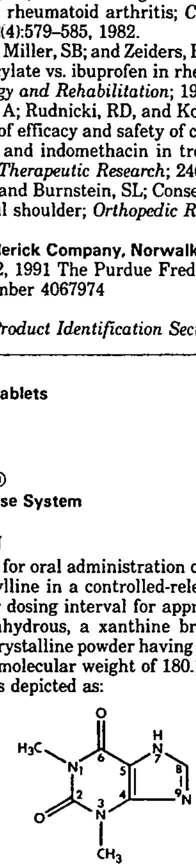
UNICONTIN®

Controlled-Release System

DESCRIPTION

Uniphyl Tablets for oral administration contain 400 mg anhydrous theophylline in a controlled-release system which allows a 24-hour dosing interval for appropriate patients.

Theophylline anhydrous, a xanthine bronchodilator, is a white, odorless crystalline powder having a bitter taste. Theophylline has a molecular weight of 180.18, represented by $C_7H_8N_4O_2$ and is depicted as:



INACTIVE INGREDIENTS

Cetostearyl alcohol, Hydroxyethyl cellulose, Magnesium stearate, Povidone and Talc.

CLINICAL PHARMACOLOGY

Theophylline directly relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels, thus acting mainly as a bronchodilator and smooth muscle relaxant. It has also been demonstrated that aminophylline has a potent effect on diaphragmatic contractility in normal persons and may then be capable of reducing fatigability and thereby improve contractility in patients with chronic obstructive airways disease. The exact mode of action remains unsettled. Although theophylline does cause inhibition of phosphodiesterase with a resultant increase in intracellular cyclic AMP, other agents similarly inhibit the enzyme producing a rise of cyclic AMP but are unassociated with any demonstrable bronchodilation. Other mechanisms proposed include an effect on translocation of intracellular calcium; prostaglandin antagonism; stimulation of catecholamines endogenously; inhibition of cyclic guanosine monophosphate metabolism and adenosine receptor antagonism. None of these mechanisms have been proven, however.

In vitro, theophylline has been shown to act synergistically with beta agonists and there are now available data which do demonstrate an additive effect *in vivo* with combined use.

Pharmacokinetics: The half-life of theophylline is influenced by a number of known variables. It may be prolonged in chronic alcoholics, particularly those with liver disease (cirrhosis or alcoholic liver disease), in patients with congestive heart failure, and in those patients taking certain other drugs (see PRECAUTIONS, Drug Interactions). Newborns and neonates have extremely slow clearance rates compared to older infants and children, i.e., those over 1 year. Older children have rapid clearance rates while most non-smoking adults have clearance rates between these two extremes. In premature neonates the decreased clearance is related to oxidative pathways that have yet to be established.

Conventional Theophylline Immediate-Release Elimination Characteristics

	Half-Life (in hours)	
	Range	*Mean*
Children	1–9	3.7
Adults	3–15	7.7

In cigarette smokers (1–2 packs/day) the mean half-life is 4–5 hours, much shorter than in non-smokers. The increase in clearance associated with smoking is presumably due to stimulation of the hepatic metabolic pathway by components of cigarette smoke. The duration of this effect after cessation of smoking is unknown but may require 6 months to 2 years before the rate approaches that of a non-smoker.

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 Uniphyl Tablets. The relative bioavailability of Uniphyl 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 Uniphyl 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 Uniphyl Tablets given once daily in the morning and a widely-used approved controlled-release BID product administered as two 200 mg tablets given 12 hours apart. The pharmacokinetic parameters obtained for Uniphyl 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:

	Uniphyl Tablets 800 mg Q 24 h ± S.D.	Reference Drug 400 mg Q 12 h ± 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

Bioavailability was calculated to be 104 ± 18% (S.D.) for the 24-hour period with Uniphyl Tablets once daily as compared with the reference drug given twice daily, as shown above.

In a single-dose crossover study, two 400 mg Uniphyl 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 ± 83.0 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 Uniphyl was 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 ± 4.5
Cmin (mcg/ml)	5.5 ± 2.9	5.0 ± 2.5
Tmax (hours)	8.1 ± 3.7	10.1 ± 4.1

The absorption characteristics of Uniphyl Tablets (theophylline, anhydrous) have been extensively studied. A steady-state crossover bioavailability study in 22 normal males compared two Uniphyl 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 Uniphyl 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.

Single-dose studies in which subjects were fasted for twelve (12) hours prior 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 400 mg tablets in the morning, compared dosing under 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 fed 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 ± 65.3 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 Uniphyl 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 Uniphyl 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 cg/ml, Tmax = 11.8 ± 2.2 hours. In the fasting arm, the armacokinetic parameters (normalized to 800 mg) were UC = 146.4 ± 40.9 mcg hr/ml, Cmax = 6.7 ± 1.7 mcg/ml, Tmax = 7.3 ± 2.2 hours.

Thus, it has been established that while there is reduced bioavailability with fasting there is no failure of the delivery system leading to a sudden and unexpected release of a large quantity of theophylline with Uniphyl Tablets even when they are administered with a high fat, high calorie meal.

These studies demonstrate that as long as subjects were either consistently fed or consistently fasted, there is similar bioavailability with once-daily administration of Uniphyl Tablets, whether dosed in the morning or evening.

The AUC and Cmax are dose-dependent and will increase by upward dosage adjustment with Uniphyl Tablets. Patients who are fast theophylline metabolizers (clearance-greater than 5 L/hr) may not be suitable candidates for once-daily dosing. Those patients who are not well-maintained on recommended once-a-day therapy are likely to be better controlled when theophylline is administered in divided doses.

INDICATIONS AND USAGE

For relief and/or prevention of symptoms from asthma and reversible bronchospasm associated with chronic bronchitis and emphysema.

CONTRAINDICATIONS

This product is contraindicated in individuals who have shown hypersensitivity to its components. It is also contraindicated in patients with active peptic ulcer disease, and in individuals with underlying seizure disorders (unless receiving appropriate anticonvulsant medication).

WARNINGS

Serum levels above 20 mcg/ml are rarely found after appropriate administration of the recommended doses. However, in individuals in whom theophylline plasma clearance is reduced for any reason, even conventional doses may result in increased serum levels and potential toxicity. Reduced theophylline clearance has been documented in the following readily identifiable groups: 1) patients with impaired er function; 2) patients over 55 years of age, particularly les and those with chronic lung disease; 3) those with car- ac failure from any cause; 4) patients with sustained high fever; 5) neonates and infants under 1 year of age; and 6) those patients taking certain drugs (see PRECAUTIONS, Drug Interactions). Frequently, such patients have markedly prolonged theophylline serum levels following discontinuation of the drug. Decreased theophylline clearance may occur following immunization for influenza, with active influenza, or other viral illnesses, and also with high fever for prolonged periods. This may be specially true in infants and the elderly.

Reduction of dosage and laboratory monitoring are especially appropriate in the above individuals.

Serious side effects such as ventricular arrhythmias, convulsions or even death may appear as the first sign of toxicity without any previous warning. Elderly patients with serum concentrations above 20 μg/ml are more likely to experience serious side effects such as ventricular arrhythmias or convulsions than are younger patients. Less serious signs of theophylline toxicity (i.e., nausea and restlessness) may occur frequently when initiating therapy, but are usually transient; when such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 mcg/ml. Stated differently: *serious toxicity is not reliably preceded by less severe side effects.* A serum concentration measurement is the only reliable method of predicting potentially life-threatening toxicity.

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

Theophylline products may cause or worsen arrhythmias and any significant change in rate and/or rhythm warrants monitoring and further investigation.

Studies in laboratory animals (minipigs, rodents and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

PRECAUTIONS

General: On the average, theophylline half-life is shorter in cigarette and marijuana smokers than in non-smokers, but smokers can have half-lives as long as non-smokers. Theophylline should not be administered concurrently with other xanthines. Use with caution in patients with hypoxemia, hypertension, or those with history of peptic ulcer. Theophylline may occasionally act as a local irritant to G.I. tract although gastrointestinal symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 mcg/ml.

Information for Patients: The physician should reinforce the importance of taking only the prescribed dose and observing the time interval between doses. Information relating to taking Uniphyl in relation to meals or fasting should be provided. All patients should be asked to report side effects which occur at any time or recurrence of symptoms, especially toward the end of a 24-hour dosing interval. Uniphyl Tablets are not to be chewed or crushed.

Laboratory Tests: Serum levels should be monitored periodically to determine the theophylline level associated with observed clinical response and as the method of predicting toxicity. For such measurements, the serum sample should be obtained at the approximate time of the expected peak concentration, i.e., about 9 hours after administration in the morning or about 12 hours after administration in the evening. It is important that the patient will not have missed or taken additional doses during the previous 48 hours and that dosing intervals will have been reasonably equally spaced. DOSAGE ADJUSTMENT BASED ON SERUM THEOPHYLLINE MEASUREMENTS WHEN THESE INSTRUCTIONS HAVE NOT BEEN FOLLOWED MAY RESULT IN RECOMMENDATIONS THAT PRESENT RISK OF TOXICITY TO THE PATIENT.

Drug Interactions: Toxic synergism with ephedrine has been documented and may occur with other sympathomimetic bronchodilators. In addition, the following drug interactions have been demonstrated:

Theophylline with:	
Allopurinol (high-dose)	Increased serum theophylline levels
Cimetidine	Increased serum theophylline levels
Ciprofloxacin	Increased serum theophylline levels
Erythromycin, Troleandomycin	Increased serum theophylline levels
Lithium carbonate	Increased renal excretion of lithium
Norfloxacin	Increased serum theophylline levels
Oral Contraceptives	Increased serum theophylline levels
Phenytoin	Decreased theophylline and phenytoin serum levels
Propranolol	Increased serum theophylline levels
Rifampin	Decreased serum theophylline levels

Drug-Food Interactions: The absorption characteristics of Uniphyl® Tablets (theophylline, anydrous) have been studied and are enhanced by co-administration with food. In two single-dose studies in which subjects were given Uniphyl with either a standardized breakfast or a high fat content meal, bioavailability under the fasting conditions were 61% and 66% respectively in comparison to under the fed condition. (SEE CLINICAL PHARMACOLOGY, Pharmacokinetics).

A drug-food effect, if any, would likely have its greatest clinical significance when high theophylline serum levels are being maintained and/or when large single doses (greater than 13 mg/kg or 900 mg) of a controlled-release theophylline product are given.

Drug-Laboratory Test Interactions: Currently available analytical methods, including high pressure liquid chromatography and immunoassay techniques, for measuring serum theophylline levels are specific. Metabolites and other drugs generally do not affect the results. Other new analytic methods are also now in use. The physician should be aware of the laboratory method used and whether other drugs will interfere with the assay for theophylline.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term carcinogenicity studies have not been performed with theophylline.

Chromosome-breaking activity was detected in human cell cultures at concentrations of theophylline up to 50 times the therapeutic serum concentrations in humans. Theophylline was not mutagenic in the dominant lethal assay in male mice given theophylline intraperitoneally in doses up to 30 times the maximum daily human oral dose.

Studies to determine the effect on fertility have not been performed with theophylline.

Pregnancy: Category C—Animal reproduction studies have not been conducted with theophylline. It is also not known whether theophylline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Xanthines should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Theophylline is distributed into breast milk and may cause irritability or other signs of toxicity in nursing infants. Because of the potential for serious adverse reactions in nursing infants from theophylline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children under 12 years of age have not been established with 400 mg Uniphyl Tablets.

ADVERSE REACTIONS

The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency. The most consistent adverse reactions are usually due to overdosage.

1. *Gastrointestinal:* nausea, vomiting, epigastric pain, hematemesis, diarrhea.
2. *Central nervous system:* headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.
3. *Cardiovascular:* palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, ventricular arrhythmias.
4. *Respiratory:* tachypnea.
5. *Renal:* potentiation of diuresis.
6. *Others:* alopecia, hyperglycemia, inappropriate ADH syndrome, rash, Stevens-Johnson syndrome.

OVERDOSAGE

Management: It is suggested that the management principles (consistent with the clinical status of the patient when first seen) outlined below be instituted and that simultaneous contact with a Regional Poison Control Center be established. In this way, both updated information and individualization regarding required therapy may be provided.

1. When potential oral overdose is established and seizure has not occurred:
   a) If patient is alert and seen within the early hours after ingestion, induction of emesis may be of value. Gastric lavage has been demonstrated to be of no value in influencing outcome in patients who present more than 1 hour after ingestion.
   b) Administer a cathartic. Sorbitol solution is reported to be of value.
   c) Administer repeated doses of activated charcoal and monitor theophylline serum levels.
   d) Prophylactic administration of phenobarbital has been shown to increase the seizure threshold in laboratory animals, and administration of this drug can be considered.
2. If patient presents with a seizure:
   a) Establish an airway.
   b) Administer oxygen.
   c) Treat the seizure with intravenous diazepam, 0.1 to 0.3 mg/kg up to 10 mg. If seizures cannot be controlled, the use of general anesthesia should be considered.
   d) Monitor vital signs, maintain blood pressure and provide adequate hydration.

Continued on next page

Purdue Frederick—Cont.

3. If post-seizure coma is present:
a) Maintain airway and oxygenation.
b) If post-seizure coma is a result of oral medication, follow above recommendations to prevent absorption of the drug, but intubation and lavage will have to be performed instead of inducing emesis, and the cathartic and charcoal will need to be introduced via a large bore gastric lavage tube.
c) Continue to provide full supportive care and adequate hydration until the drug is metabolized. In general, drug metabolism is sufficiently rapid so as not to warrant dialysis. If repeated oral activated charcoal is ineffective (as noted by stable or rising serum levels) charcoal hemoperfusion may be indicated.

DOSAGE AND ADMINISTRATION

Uniphyl 400 mg Tablets can be taken once a day in the morning or evening. It is recommended that Uniphyl be taken with meals. Patients should be advised that if they choose to take Uniphyl with food it should be taken consistently with food and if they take it in a fasted condition it should routinely be taken fasted. It is important that the product whenever dosed be dosed consistently with or without food.

Effective use of theophylline (i.e., the concentration of drug in the serum associated with optimal benefit and minimal risk of toxicity) is considered to occur when the theophylline concentration is maintained from 10 to 20 mcg/ml. The early studies from which these levels were derived were carried out in patients immediately or shortly after recovery from acute exacerbations of their disease (some hospitalized with status asthmaticus).

Although the 20 mcg/ml level remains appropriate as a critical value (above which toxicity is more likely to occur) for safety purposes, additional data are now available which indicate that the serum theophylline concentrations required to produce maximum physiologic benefit may, in fact, fluctuate with the degree of bronchospasm present and are variable. Therefore, the physician should individualize the range appropriate to the patient's requirements, based on both symptomatic response and improvement in pulmonary function.

As with all sustained-release theophylline products, Uniphyl Tablets are for chronic or long-term use and are not intended for initial treatment in a patient with acute symptoms.

If it is not possible to obtain serum level determinations, restriction of the daily dose (in otherwise healthy adults) to not greater than 13 mg/kg/day, to a maximum of 900 mg, in divided doses will result in relatively few patients exceeding serum levels of 20 mcg/ml and the resultant greater risk of toxicity.

Caution should be exercised in younger children who cannot complain of minor side effects. Older adults, those with cor pulmonale, congestive heart failure, and/or liver disease may have unusually low dosage requirements and thus may experience toxicity at the maximal dosage recommended below.

Theophylline does not distribute to fatty tissue. Dosage should be calculated on the basis of lean (ideal) body weight where mg/kg doses are presented.

Frequency of Dosing: Patients who clear theophylline normally or relatively slowly, e.g., non-smokers, may be reasonable candidates for taking Uniphyl Tablets once-daily. However, certain patients, such as the young, smokers and some non-smoking adults are likely to metabolize theophylline more rapidly and may require dosing at 12 hour intervals. Such patients may experience symptoms of bronchospasm toward the end of a once daily dosing interval and/or require a high daily dose (higher than those recommended in labeling) and are more likely to experience relatively wide peak to trough differences in serum theophylline concentrations.

Dosage Guidelines:

WARNING: DO NOT ATTEMPT TO MAINTAIN ANY DOSE THAT IS NOT WELL TOLERATED.

Dosage guidelines are approximations only, and the wide range of clearance of theophylline among individuals (particularly those with concomitant disease) makes indiscriminate usage hazardous. When appropriate, dosage should be calculated on the basis of lean body weight where mg/kg doses are to be prescribed since theophylline does not distribute into fatty tissue.

I. *INITIATION OF THERAPY WITH UNIPHYL TABLETS*

a. *Stabilized Patients (12 years of age or older)*
Individuals who are taking an immediate-release or controlled-release theophylline product may be transferred to once-daily administration of 400 mg Uniphyl Tablets on a mg-for-mg basis. For example, a patient stabilized on 400 mg twice daily (800 mg total daily dose) should be given two 400 mg Uniphyl Tablets as a single daily dose of 800 mg in either the morning or the evening.
It must be recognized that the peak and trough serum theophylline levels produced by the once daily dosage may vary from those produced by the previous product and/or regimen.

b. *Initiation of Theophylline Dosing*
Adult patients and children 12 years of age and over not currently receiving theophylline may be titrated using an immediate or sustained release theophylline product, which can be adjusted in small dosage increments. Patients titrated to a total daily dose of approximately 400, 600, 800, 1,000 or 1,200 mg may be transferred to once-daily dosage with 400 mg Uniphyl Tablets as is described in (a) above.

II. *TITRATION AND DOSE ADJUSTMENT*

a. *When Serum Levels Are Measured*
After 4 days therapy with Uniphyl Tablets, steady-state should have been achieved, and approximate peak serum theophylline concentration samples should be determined from blood samples obtained about 9 hours after administration in the morning or about 12 hours after administration in the evening. When taken in the evening with supper it may not be possible to get blood levels within 12 hours following the daily dose. Under these circumstances blood levels should be measured as early in the morning as practical, recognizing that such levels may be somewhat lower than the actual peak achieved. Trough concentration should be taken just prior to the administration of the next dose. It is important that the patient not have missed or added any dose during the previous 72 hours, and that the dosing intervals remain relatively constant. DOSAGE ADJUSTMENT BASED ON MEASUREMENTS WHEN THESE INSTRUCTIONS HAVE NOT BEEN FOLLOWED MAY RESULT IN TOXICITY.

b. *When Serum Levels Are Not Measured*
In the absence of laboratory facilities for determining serum theophylline concentration levels, clinical judgment should be followed.
- The original total once-daily dose should continue if it is well tolerated and the clinical response is satisfactory.
- If adverse reactions occur, decrease the dose as stated below.

If a patient is better controlled on another regimen than on a once daily regimen, the patient should be maintained on the more effective regimen.

c. *Increasing the Dose of Uniphyl Tablets*
If patient response with Uniphyl Tablets is unsatisfactory and/or the observed serum theophylline concentration range is too low, the patient should be transferred to an immediate or controlled-release (BID) theophylline schedule and dosage increased at recommended intervals as follows:

Serum Theophylline (mcg/ml)	*Directions*
Too low	Increase dosage at 3 day intervals by 25%. The serum concentration may be rechecked at appropriate intervals, but at least at the end of the adjustment period.*

When the patient's condition is otherwise clinically stable and none of the recognized factors which alter elimination are present, measurement of serum levels need be repeated only every 6 to 12 months.
*The total daily dose may need to be administered at more frequent intervals if symptoms occur repeatedly at the end of a dosing interval.

d. *Decreasing the Dose of Uniphyl Tablets*
Serum theophylline values above 20 mcg/ml require decreasing the daily dose unless such dose is required to maintain the patient and is well-tolerated. Dosage may be reduced by transferring the patient to an immediate or controlled-release (BID) theophylline product and making adjustments. Peak and trough measurements should be taken 3 days after each decrease in dosage.

Serum Theophylline (mcg/ml)	*Directions*
20 to 25	Decrease dose by about 10%
25 to 30	Skip next dose and decrease subsequent doses by about 25%
Over 30	Skip next 2 doses and decrease subsequent doses by 50%

Finer adjustments in dosage may be needed for some patients.

III. *Maintenance Therapy*
Careful clinical titration is important to assure patient acceptance and safety of the medication. Patients, when stabilized as established by serum theophylline concentration or respiratory function, usually remain controlled without further dosage adjustment. It should be borne in mind, however, that for reasons stated in the PRECAUTIONS and WARNINGS sections, dosage adjustments may be necessary. Serum theophylline levels should be measured periodically (at 6 to 12-month intervals) even in clinic
controlled patients.
The elderly as well as patients with congestive h
failure, cor pulmonale, and/or liver disease may h
unusually low dosage requirements and thus r
experience toxicity even at the dosages recommen
above.

WARNING: DO NOT MAINTAIN ANY DOSE THAT NOT TOLERATED.

HOW SUPPLIED

Uniphyl (theophylline, anhydrous) 400 mg scored C
trolled-Release Tablets are supplied in white-opaque pla
bottles, containing 100 tablets [NDC 0034-7004-80] or
tablets [NDC 0034-7004-70] or in unit dose packaging with
tablets per card [NDC 0034-7004-10]; ten cards are packe
each carton; 10 cartons are packed in each shipper.
Each round, white tablet bears the symbols PF on one s
and is marked U400 on the other side.
Store tablets at controlled room temperature 15° to 3
(59–86°F).

CAUTION: Federal law prohibits dispensing without p
scription.

The Purdue Frederick Company
Norwalk, CT 06850-3590

U.S. Patent Numbers 4,235,870 and 4,366,310
February 17, 1993 O13

Shown in Product Identification Section, page 323

EDUCATIONAL MATERIAL

Audio Visuals—Booklets—Samples

Q & A: "Genital Warts—More Common Than You Thin
booklet (Alferon N Injection)
Pain Assessment Program (medical forms and patient boo
lets) (MS Contin)
Cancer Pain Management Slide Program (MS Contin)
"Up-To-Date Answers About Pain Medications" booklet f
patient education. (MS Contin)
"Home Care of the Hospice Patient"—Guide to caring f
cancer patients. (English/Spanish) (MS Contin)
Pain Assessment Questionnaire (MS Contin)
Dosing Conversion Reference (MS Contin)
Controlling Cancer Pain—Video film (MS Contin)
Arthritis Exercise Pads (English and Spanish) (Trilisate)
Arthritis Assessment Questionnaire (Trilisate)
"Nocturnal Asthma"—Understanding and Managing th
Disease at night" (Uniphyl)
Respiratory Assessment Questionnaire (English and Spa
ish) (Uniphyl)
Patient Dosing Instructions Sheets (English and Spanish
(Uniphyl)
Asthma—A Nocturnal Video Film (Uniphyl)
"Protect Your Family From Germs" patient-aid bookl
(English and Spanish) (Betadine)
Samples of Betadine First Aid and Betadine Feminin
Hygiene Products.
"Knowing All About Women's Health" Patient Brochure.
"Fem-Facts®" booklets (Facts about Vaginitis Symptom
for Patients) (Betadine)
"Betadine Microbicides and the AIDS Virus" brochure
"How You Can Make It Feel Better"—Guide to Caring fo
Cuts, Burns and Scrapes (Betadine)
"Helping Your Wounds Heal"—Care of Cuts, Scrapes, Mino
Burns (Betadine)
Spanning the Spectrum in Hospital Infection Control Vide
tape film (Betadine)
"Fiber and Your Health" booklet (Fibermed)
Senokot Constipation Assessment In-Service Training Vid
eotape "Current Concepts in Constipation Management"
Senokot Family Dosage Card (Senokot)
Senokot Patient Information Booklet "When a common sid
effect of many medications becomes a problem—Drug
Induced Constipation" (Senokot)
Senokot Laxative Protocol Pad (Senokot)

Products are categorized
in the **BLUE** section.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBERS:

89-822 & 89-823/ S-001; S-002; S-004; S-005; S-008

CORRESPONDENCE

2/4/02
1W

Redacted 1

Page(s) of trade secret and /or confidential commercial information

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033
TELEPHONE: (908) 298-4000

March 29, 2001

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation & Research
Document Control Room (HFD-601)
Metro Park North 2, Room 286
7500 Standish Place
Rockville, MD 20857

ANDA 89-822
ANDA 89-823
UNI-DUR (theophylline)
Extended Release Tablets

NDA NO. 89823 REF. NO. SLOO8A1
NDA SUPPL FOR Labeling Supp

SUBJECT: SPECIAL SUPPLEMENT-CHANGES BEING EFFECTED

Dear Mr. Buehler:

Schering Corporation is submitting a revised Product Information Sheet for UNI-DUR (theophylline) Extended Release Tablets. The revised Product Information Sheet contains the addition of "St. Johns Wort (Hypericum perforatum)" to the "Information for Patients" and "Drug Interaction" section Table II. The revised text in the "Information for Patients" section reads as follows:

> The herbal remedy St. John's Wort (Hypericum perforatum) should not be taken at the same time as theophylline. If they are already taking St. John's Wort they should consult their physician before stopping the St. John's Wort preparations.

The revised text in the "Drug Interaction" section Table II reads as follows:

Table II. Clinically significant drug interactions with theophylline (cont.)

Drug	Type of Interaction
St. John's Wort (Hypericum perforatum)	Decrease in theophylline plasma concentration

The inclusion of this drug interaction is the result of a review by our Drug Safety Surveillance Group, and a discussion by our Clinical and Preclinical Safety Surveillance Committee. Based on these discussions, there was a decision that this additional drug interaction should be incorporated into our labeling as changes

Being Effected per CFR Title 21 314.70 (c)(2)(i). Included in this submission is the medical rational and supporting documentation for the new drug interaction (**Attachment 1**). Additionally, we have provided 12 copies of the final printed labeling with this new sentence highlighted for your convenience (**Attachment 2).**

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Christine Nielsens /for

Mary Jane Nehring
Senior Director, Marketed Products
Support and Training
Worldwide Regulatory Affairs

CV:js
Attachments

SCHERING CORPORATION

GALLOPING HILL ROAD KENILWORTH, N. J. 07033

CABLES: SCHERING KENILWORTH
TELEX: 138316
138280
TELEPHONE: (908) 298-4000

April 30, 1997

Mr. Jerry Phillips, Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation & Research
MAN-II, Room 150
7500 Standish Place
Rockville, MD 20855

ANDA 89-822/S-005
ANDA 89-823/S-005
UNI-DUR (theophylline)
Extended-release Tablets

SL005AL
NDA SUPPL AMENDMENT

FPL satisfactory
contains 003
S-004 information
C. Holquist 5/6/97

SUBJECT: AMENDMENT TO PENDING SUPPLEMENT S-005

Dear Mr. Phillips,

We refer to our April 2, 1997 amendment to pending supplement S-005 which included final printed labeling in response to your February 18, 1997 approvable letter. This labeling supplement provided for the addition of ritonavir to the table of clinically significant drug interactions contained in the PRECAUTIONS section of the package insert.

The purpose of this submission is to correct an inadvertent omission in the FPL submitted on April 2. On April 30, Ms. Carol Hulquist of the Division informed us via telephone that the FPL did not include the ritonavir drug interaction information, and requested that we submit corrected package insert labeling. Twelve copies of the final printed insert are enclosed. We apologize for any confusion caused by this error.

Please be advised that the material and data contained in this submission are considered confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j), as well as the FDA regulations.

RECEIVED
MAY 01 1997
GENERIC DRUGS

Sincerely,

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

MM:js
Enclosures

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

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 >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 >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, eg, diazepam, in increments of 0.1-0.2 mg/kg every 1-3 minutes until seizures are terminated. Repetitive seizures should be treated with a loading dose of phenobarbital (20 mg/kg infused over 30-60 minutes). Animal studies and case reports of theophylline overdose in humans 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, eg, patients with acute overdoses and serum theophylline concentrations >100 mcg/mL or chronic overdosage in patients >60 years of age with serum theophylline concentrations >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 (eg, transfer of a high-risk patient from one healthcare facility to another for extracorporeal removal) and clinical circumstances that significantly interfere with efforts to enhance theophylline clearance (eg, 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 (ie, markedly increases the LD_{50}). 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 1-2 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, 2-4 hours later, and then at sufficient intervals, eg, 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 (eg, 0.5 mg/kg up to 20 g, every 2 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 >20 <30 mcg/mL
1. Administer a single dose of oral activated charcoal.
2. Monitor the patient and obtain a serum theophylline concentration in 2-4 hours to ensure that the concentration is not increasing.

B. Serum Concentration >30 <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 2-4 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 >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 2-4 hours to gauge the effectiveness of therapy and to guide further treatment decisions.

Chronic Overdosage

A. Serum Concentration >20 <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 2-4 hours to ensure that the concentration is not increasing.

B. Serum Concentration >30 mcg/mL in patients <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 2-4 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 >30 mcg/mL in patients ≥ 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 2-4 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 5-10 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.

UNI-DUR®
(theophylline)
Extended-release
Tablets

Key Pharmaceuticals, Inc.
Kenilworth, NJ 07033 USA

Rev. 3/97

Table II. Clinically significant drug interactions with theophylline.* *(cont.)*

Drug	Type of Interaction	Effect**
Norfloxacin	Increases serum theophylline levels.	
Ofloxacin	Increases serum theophylline levels.	
Pancuronium	Theophylline may antagonize non-depolarizing neuromuscular blocking effects; possibly due to phospho-diesterase inhibition.	Larger dose of pancuronium may be required to achieve neuromuscular blockade.
Pentoxifylline	Decreases theophylline clearance.	30% increase
Phenobarbital (PB)	Similar to aminoglutethimide.	25% decrease after 2 weeks of concurrent PB.
Phenytoin	Phenytoin increases theophylline clearance by increasing microsomal enzyme activity. Theophylline decreases phenytoin absorption.	Serum theophylline *and* phenytoin concentrations decrease about 40%.
Propafenone	Decreases theophylline clearance and pharmacologic interaction.	40% increase. Beta$_2$-blocking effect may decrease efficacy of theophylline.
Propranolol	Similar to cimetidine and pharmacologic interaction.	100% increase. Beta$_2$-blocking effect may decrease efficacy of theophylline.
Rifampin	Increases theophylline clearance by increasing cytochrome P450 1A2 and 3A3 activity.	20%-40% decrease
Ritonavir	Increases theophylline clearance (mechanism unknown)	43% decrease in AUC
Sucralfate	Reduced absorption of theophylline.	
Sulfinpyrazone	Increases theophylline clearance by increasing demethylation and hydroxylation. Decreases renal clearance of theophylline.	20% decrease
Tacrine	Similar to cimetidine, also increases renal clearance of theophylline.	90% increase
Thiabendazole	Decreases theophylline clearance.	190% increase
Ticlopidine	Decreases theophylline clearance.	60% increase
Troleandomycin	Similar to erythromycin.	33%-100% increase depending on troleandomycin 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.

Drug/Food Interactions:
The extent of theophylline absorption from UNI-DUR® Extended-release Tablets is similar when administered fasting or immediately after a high-fat content breakfast. However, the time to peak concentration was delayed following the high-fat content breakfast (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**). This breakfast contained 729 total kilocalories of which 55% were derived from 45 g of fat; and it consisted of two scrambled eggs, two strips of bacon, one slice of toast with 1 pat of butter, 3 oz. of hash brown potatoes, and 180 mL of whole milk. 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 (eg, cefazolin, cephalothin), however, may interfere with certain HPLC techniques. Caffeine and xanthine metabolites in 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 30-150 mg/kg) and rats (oral doses 5-75 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 B6C3F$_1$ mice at oral doses of 120, 270, and 500 mg/kg (approximately 1.0-3.0 times the human dose on a mg/m^2 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 B6C3F$_1$ mice at oral doses of 40-300 mg/kg (approximately 2.0 times the human dose on a mg/m^2 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 nonrodents (eg, 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 recommended human dose on a mg/m^2 basis or CD-1 rats at oral doses up to 260 mg/kg, approximately 3.0 times the recommended human dose on a mg/m^2 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 10-20 mcg/mL of theophylline a day is likely to receive 10-20 mg of theophylline per day. Serious adverse effects in the infant are unlikely unless the mother has toxic serum theophylline concentrations.

Pediatric Use:
Safety and effectiveness of UNI-DUR Extended-release Tablets in pediatric patients under 12 years of age have not been established. Other theophylline formulations, however, are safe and effective for the approved indications in pediatric patients under the age of 12. 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 IV**).

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 <10 mcg/mL (see **DOSAGE AND ADMINISTRATION**). Theophylline doses greater than 400 mg/day should be prescribed with caution in elderly patients.

ADVERSE REACTIONS

Adverse reactions associated with theophylline are generally mild when peak serum theophylline concentrations are <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 (eg, >300 mg/day in adults and >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 IV**). In a small percentage of patients (<3% of children and <10% of adults), the caffeine-like adverse effects persist during maintenance therapy, even at peak serum theophylline concentrations within the therapeutic range (ie, 10-20 mcg/mL). Dosage reduction may alleviate the caffeine-like adverse effects in these patients; however, persistent adverse effects should result in a re-evaluation of the need for continued theophylline therapy and the potential therapeutic benefit of alternative treatment.

Other adverse reactions that have been reported to occur at serum theophylline concentrations less than 20 mcg/mL include diarrhea, irritability, restlessness, fine skeletal muscle tremors, alopecia, muscle twitching/spasms, palpitations, rash, reflex hyperexcitability, transient diuresis, and ventricular arrhythmias. Whether or not theophylline caused these reported events is not known. In patients with hypoxia secondary to COPD, multifocal atrial tachycardia and flutter have been reported at serum theophylline concentrations ≥ 15 mcg/mL. There have been a few isolated reports of seizures at serum theophylline concentrations <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 <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 <20 mcg/mL have generally been milder than seizures associated with excessive serum theophylline concentrations resulting from an overdose (ie, they have generally been transient, often stopped without anticonvulsant therapy, and did not result in neurological residua).

Table III. 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 (n=157)	Study 2 (n=14)	Study 1 (n=92)	Study 2 (n=102)
Asymptomatic	NR**	0	NR**	6
Gastrointestinal				
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 with hemodynamic instability	7	14	40	0
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 >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 >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 (eg, 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,* ie, ingestion of a single large excessive dose (>10 mg/kg) as occurs in the context of an attempted suicide or isolated medication error, and (2) *chronic overdosage,* ie, 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 caregiver 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 20-30 mcg/mL range and 3% were >30 mcg/mL. Approximately two thirds of the patients with serum theophylline concentrations in the 20-30 mcg/mL range had one or more manifestations of toxicity while >90% of patients with serum theophylline concentrations >30 mcg/mL were clinically intoxicated. Similarly, in other reports, serious toxicity from theophylline is seen principally at serum concentrations >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 >100 mcg/mL. After a chronic overdosage, generalized seizures, life-threatening cardiac arrhythmias, and death may occur at serum theophylline concentrations >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 >60 years are at the greatest risk for severe toxicity and mortality after a chronic overdosage. Pre-existing or concurrent disease may also significantly increase the susceptibility of a patient to a particular toxic manifestation, eg, 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.

DOSAGE AND ADMINISTRATION

The extent of absorption of theophylline from UNI-DUR Tablets when administered fasting or immediately after a high-fat content breakfast is similar. However, the time to peak concentration is delayed (see **PRECAUTIONS, Drug/Food Interactions**).

Effective use of theophylline (ie, the concentration of drug in the serum associated with optimal benefit and minimal risk of toxicity) is considered to occur when the theophylline concentration is maintained from 10 to 15 mcg/mL.

Patients who clear theophylline normally or relatively slowly, eg, nonsmokers, may be reasonable candidates for taking UNI-DUR Tablets once daily. However, certain patients, such as the young, smokers, and some nonsmoking adults are likely to metabolize theophylline more rapidly and may require dosing at 12-hour intervals. Such patients may experience symptoms of bronchospasm toward the end of a once-daily dosing interval and/or require a higher daily dose (higher than those recommended in labeling) and are more likely to experience relatively wide peak to trough differences in serum theophylline concentrations.

UNI-DUR Tablets may be administered either in the morning or in the evening.

UNI-DUR Tablets *should not be chewed or crushed.*

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 10-20 mcg/mL range varies fourfold among otherwise similar patients in the absence of factors known to alter theophylline clearance (eg, 400-1600 mg/day in adults <60 years old and 10-36 mg/kg/day in children 1-9 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/day in adults <60 years or 22 mg/kg/day in children 1-9 years, the steady-state peak serum theophylline concentration will be <10 mcg/mL in about 30% of patients, 10-20 mcg/mL in about 50%, and 20-30 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 IV**). 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, Monitoring Serum Theophylline Concentrations**, and **DOSAGE AND ADMINISTRATION, Table V**). Healthcare providers should instruct patients and caregivers 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, eg, every 24 hours.

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

Table IV contains theophylline dosing titration schema recommended for patients in various age groups and clinical circumstances. **Table V** 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 dose adjustments in order to decrease the risk of potentially serious adverse events associated with unexpected large increases in serum theophylline concentration.**

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

A. Children (12-15 years) and adults (16-60 years) without risk factors for impaired clearance.

Titration Step	*Children <45 kg*	*Children >45 kg and adults*
1. Starting dosage:	12-14 mg/kg/day up to a maximum of 300 mg/day administered QD*	300-400 mg/day[1] administered QD*
2. After 3 days, *if tolerated*, increase dose to:	16 mg/kg/day up to a maximum of 400 mg/day administered QD*	400-600 mg/day[1] administered QD*
3. After 3 more days, *if tolerated*, increase dose to:	20 mg/kg/day up to a maximum of 600 mg/day administered QD*	As with all theophylline products, doses greater than 600 mg should be titrated according to blood level (see **Table V**).

B. **Patients With Risk Factors For Impaired Clearance, The Elderly (>60 Years), And Those In Whom It Is Not Feasible To Monitor Serum Theophylline Concentrations:**

In children 12-15 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 ≥16 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 12 hours) to prevent breakthrough symptoms resulting from low trough concentrations before the next dose.

[1]If caffeine-like adverse effects occur, then consideration should be given to a lower dose and titrating the dose more slowly (see **ADVERSE REACTIONS**).

Table V. Dosage adjustment guided by serum theophylline concentration.

Peak Serum Concentration	Dosage Adjustment
<9.9 mcg/mL	If symptoms are not controlled and current dosage is tolerated, increase dose about 25%. Recheck serum concentration after 3 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- to 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.¶
20-24.9 mcg/mL	Decrease dose by 25% even if no adverse 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).
>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 (eg, sustained fever), or a drug that interacts with theophylline is added or discontinued (see **WARNINGS**).

HOW SUPPLIED

UNI-DUR Extended-release Tablets are supplied as controlled-release tablets containing either 400 mg or 600 mg of theophylline anhydrous. They are mottled white, capsule-shaped tablets; scored on one side and debossed with the product name and strength on the other.

UNI-DUR Extended-release Tablets 400 mg are available in bottles of 100's (NDC 0085-0694-01).

UNI-DUR Extended-release Tablets 600 mg are available in bottles of 100's (NDC 0085-0814-01).

STORAGE CONDITIONS

Keep bottles tightly closed. Store between 15° and 25°C (59° and 77°F).

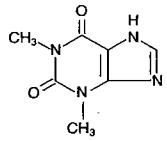
CAUTION: Federal law prohibits dispensing without prescription.

Some of the information contained in this insert (eg, information regarding pediatric patients under the age of 12) was derived from FDA's Class Labeling Guidance for Immediate-Release Theophylline Products and is intended for informational purposes only.

DESCRIPTION

UNI-DUR® Extended-release Tablets for oral administration contain 400 or 600 mg anhydrous theophylline in an extended-release system which allows a 24-hour dosing interval for appropriate patients.

Theophylline is a bronchodilator, structurally classified as a methylxanthine. It occurs as a white, odorless, crystalline powder with a bitter taste. Anhydrous theophylline has the chemical name 1*H*-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 $C_7H_8N_4O_2$ with a molecular weight of 180.17.

The inactive ingredients for UNI-DUR 400 and 600 mg Extended-release Tablets include: acacia, NF; acetone; cellulose acetate phthalate, NF; cetyl alcohol, NF; confectioner's sugar, NF; corn starch, NF; diethyl phthalate, NF; glyceryl monostearate; lactose monohydrate, NF; magnesium stearate, NF; myristyl alcohol, NF; nonpareil seeds (sugar spheres), NF; and white wax, NF.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Theophylline has two distinct actions in the airways of patients with reversible obstruction; smooth muscle relaxation (ie, bronchodilation) and suppression of the response of the airways to stimuli (ie, non-bronchodilator prophylactic effects). While the mechanisms of action of theophylline are not known with certainty, studies in animals suggest that bronchodilation is mediated by the inhibition of two isozymes of phosphodiesterase (PDE III 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 (eg, hypotension, tachycardia, headache, and emesis) and adenosine receptor antagonism (eg, 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 >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 coadministration 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 (eg, at 24-hour intervals) and periodically in patients receiving long-term therapy (eg, 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, Monitoring Serum Theophylline Concentrations** and **DOSAGE AND ADMINISTRATION**).

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)	
Age				
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 3-30 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 nonsmoking asthmatics	0.65	(0.27-1.03)	8.7	(6.1-12.8)
Elderly (>60 years)				
nonsmokers 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 nonsmoker >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)

¶ 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 1 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 nonlinear pharmacokinetics.

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

UNI-DUR Pharmacokinetics

Following the single-dose crossover administration of a 600 mg UNI-DUR Tablet to 20 healthy male subjects after an overnight fast, a peak serum theophylline concentration of 5.3 ± 1.3 mcg/mL was obtained at 13.6 ± 3.7 hours and the mean area under the curve extrapolated to infinity (AUC_{inf}) was 132.7 ± 45.1 mcg hr/mL. When taken immediately after a high-fat breakfast, the mean AUC_{inf} was 136.0 ± 36.7 mcg hr/mL with a mean peak theophylline serum level of 5.2 ± 1.5 mcg/mL at 17.1 ± 6.3 hours. While food did not affect the extent of absorption as evidenced by the similar AUC_{inf} values, food did prolong the time to peak concentration. The absorption from half tablets of the 600 mg product was also evaluated and found to be bioequivalent to that of the whole tablets. The relative extent of absorption of theophylline from the 600 mg UNI-DUR Tablet, fasting, when compared to an immediate-release theophylline tablet, was 84.3%; and for the nonfasting treatment was 88.7%.

In a separate multiple-dose study, two 400 mg UNI-DUR Tablets were compared to one 600 mg UNI-DUR Tablet. This study was a two-way, randomized, crossover multiple-dose study in 17 nonsmoking healthy males. Both products were dosed once a day in the morning after an overnight fast and 1 hour prior to a meal for 5 days. There was no significant difference in any of the pharmacokinetic parameters when corrected for dose.

The mean dose AUC_{ss} (corrected to the 600 mg dose) for the two 400 mg UNI-DUR Tablets was 179.7 ± 62.9 mcg hr/mL and for the 600 mg UNI-DUR Tablet was 170.9 ± 75.2 mcg hr/mL. The two 400 mg UNI-DUR Tablets reached dose corrected maximum serum concentration of 9.8 ± 2.6 mcg/mL and the 600 mg UNI-DUR Tablet reached a maximum of 9.7 ± 3.5 mcg/mL. The minimum concentrations were 4.9 ± 2.6 mcg/mL and 4.4 ± 2.6 mcg/mL for the two 400 mg and 600 mg UNI-DUR Tablets, respectively.

Steady-state pharmacokinetics were determined in a multiple-dose, crossover study with 24 healthy nonsmoking male subjects having an average theophylline clearance of 5.70 ± 2.36 (S.D.) liters per hour. Following an overnight fast, a UNI-DUR 600 mg Extended-release Tablet was administered once daily in the morning for 5 consecutive days. The UNI-DUR Tablet exhibited better extended-release characteristics compared with a reference extended-release q12h product (2 x 300 mg) administered once daily in the morning following an overnight fast for 5 consecutive days. The results are noted as follows (mean values ± S.D.):

	AUC_{ss} (mcg hr/mL)	C_{max} (mcg/mL)	C_{min} (mcg/mL)	T_{max} (hr)
UNI-DUR	119 ± 36	6.9 ± 2.4	3.7 ± 1.3	11.5 ± 5.7
Reference	154 ± 37	10.5 ± 2.3	2.5 ± 1.1	7.6 ± 1.7

The mean percent fluctuation [$(C_{max}-C_{min}/C_{min})$ x 100] was 130% for the once-daily UNI-DUR regimen and 389% for the reference q12h product administered once daily. The extent of theophylline absorption from UNI-DUR Tablets relative to the reference q12h product was 74.9% (95% C.I. = 67-84).

In a randomized, multiple-dose crossover study with 18 healthy male subjects, a 600 mg UNI-DUR Extended-release Tablet was administered once daily either in the morning or evening for 5 consecutive days. The theophylline AUC_{ss} for the 24-hour period following the dose given on day 5 was equivalent for morning (177 ± 89 mcg hr/mL) and evening (175 ± 76 mcg hr/mL) administration. The peak theophylline concentrations (C_{max}) at steady state were also equivalent for morning (10.6 ± 4.9 mcg/mL) and evening (10.3 ± 4.0 mcg/mL) administration.

Steady-state pharmacokinetics comparing UNI-DUR Tablets once-daily administration with twice-daily administration were determined in a multiple-dose, crossover study with 24 healthy, nonsmoking male subjects having an average theophylline clearance of 4.53 ± 1.21 (S.D.) liters per hour. Using UNI-DUR 400 mg Extended-release Tablets, a total daily theophylline dose of 800 mg was administered for 5 consecutive days either once daily as two tablets in the morning (8 AM) with a standardized breakfast or twice daily as one tablet in the morning (8 AM) with a standardized breakfast or twice daily as one tablet in the morning (8 AM) with a standardized breakfast and one tablet in the evening (8 PM). The once-daily UNI-DUR regimen was bioequivalent to the twice-daily UNI-DUR regimen. The results are noted as follows (mean values ± S.D.):

	AUC_{ss} (mcg hr/mL)	C_{max} (mcg/mL)	C_{min} (mcg/mL)	T_{max} (hr)
QD Regimen	187 ± 45	10.4 ± 2.9	6.0 ± 1.3	12.0 ± 3.7
q12h Regimen	187 ± 43	9.4 ± 2.2	8.4 ± 2.6	14.5 ± 6.6

The mean percent fluctuation [$(C_{max}-C_{min}/C_{min})$ x 100] was 78% for the once-daily UNI-DUR regimen and 17% for the twice-daily UNI-DUR regimen. The extent of theophylline absorption from the once-daily UNI-DUR regimen relative to the twice-daily UNI-DUR regimen was 100% (95% C.I. = 95-105).

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 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 (10-20 mcg/mL) due to elevated concentrations of the pharmacologically active unbound drug. Similarly, a patient with decreased theophylline binding may have a subtherapeutic 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 1 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 P450 1A2, while cytochromes P450 2E1 and P450 3A3 catalyze the hydroxylation to 1,3-dimethyluric acid. Demethylation to 1-methylxanthine appears to be catalyzed either by cytochrome P450 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 1 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 N-demethylation and hydroxylation pathways of theophylline biotransformation are capacity-limited. Due to the wide intersubject variability of the rate of theophylline metabolism, nonlinearity of elimination may begin in some patients at serum theophylline concentrations <10 mcg/mL. Since this nonlinearity 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 V**). Accurate prediction of dose-dependency of theophylline metabolism in patients *a priori* is not possible, but patients with very high initial clearance rates (ie, 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 3 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 (ie, 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, 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 immediate-release theophylline, steady state is reached in 30-65 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 4-5 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 (8-12 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 (>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 1 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 3 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, eg, about 10%, of the administered theophylline dose is excreted unchanged in the urine of children greater than 3 months of age and adults. Since little theophylline is excreted unchanged in the urine and since active metabolites of theophylline (ie, 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 (eg, 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 appear 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 1 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 or lesser temperature elevations for longer periods, are probably required to produce a clinically significant increase in serum theophylline concentrations. Children with rapid rates of theophylline clearance (ie, those who require a dose that is substantially larger than average [eg, >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
UNI-DUR Extended-release Tablets are indicated for the treatment of the symptoms and reversible airflow obstruction associated with chronic asthma and other chronic lung diseases, eg, emphysema and chronic bronchitis.

CONTRAINDICATIONS
UNI-DUR Extended-release Tablets are contraindicated in patients with a history of hypersensitivity to theophylline or other components in the product.

WARNINGS
Serious side effects such as ventricular arrhythmias, convulsions, or even death may appear as the first sign of toxicity without any recognized prior warnings. Less serious signs of theophylline toxicity (eg, nausea and restlessness) may occur frequently when initiating therapy but are usually transient. When such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 mcg/mL. Stated differently, serious toxicity is not reliably preceded by less severe side effects.

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 (peptic ulcer disease should be controlled with appropriate therapy since theophylline is known to increase peptic acid secretion)
- 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 so as to lower serum theophylline levels to within the therapeutic range 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°F 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 (eg, cimetidine, erythromycin, tacrine) or stopping a concurrently administered drug that enhances theophylline metabolism (eg, 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 should be 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, Dosage Guidelines, Table V**).

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 beta$_2$-selective agonists and systemically administered corticosteroids 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, Monitoring Serum Theophylline Concentrations**).

As the rate of theophylline clearance may be dose-dependent (ie, steady-state serum concentrations may increase disproportionately to the increase in dose), an increase in dose based upon a subtherapeutic 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 V**).

PRECAUTIONS
UNI-DUR TABLETS SHOULD *NOT* BE CHEWED OR CRUSHED AND SHOULD *BE BROKEN ONLY AT THE SCORE.*

General:
Careful consideration of the various interacting drugs (including recently discontinued medications), physiologic conditions, and other factors such as smoking 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 IV**).

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 [eg, fever (see **CLINICAL PHARMACOLOGY,** *Fever*), 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; 8 to 12 hours after a UNI-DUR dose at steady state. For most patients, steady state will be reached after 4 days of dosing with UNI-DUR Tablets 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 (ie, 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 12 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 (eg, 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 6-12 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 10-20 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 μeq/L to 800 μeq/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

WARNINGS

Serious side effects such as ventricular arrhythmias, convulsions, or even death may appear as the first sign of toxicity without any recognized prior warnings. Less serious signs of theophylline toxicity (eg, nausea and restlessness) may occur frequently when initiating therapy but are usually transient. When such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 mcg/mL. Stated differently, serious toxicity is not reliably preceded by less severe side effects.

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 (peptic ulcer disease should be controlled with appropriate therapy since theophylline is known to increase peptic acid secretion)
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 so as to lower serum theophylline levels to within the therapeutic range 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°F 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 (eg, cimetidine, erythromycin, tacrine) or stopping a concurrently administered drug that enhances theophylline metabolism (eg, 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 should be 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, Dosage Guidelines, Table V**).

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 beta$_2$-selective agonists and systemically administered corticosteroids 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, Monitoring Serum Theophylline Concentrations**).

As the rate of theophylline clearance may be dose-dependent (ie, steady-state serum concentrations may increase disproportionately to the increase in dose), an increase in dose based upon a subtherapeutic 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 V**).

PRECAUTIONS

UNI-DUR TABLETS SHOULD *NOT* BE CHEWED OR CRUSHED AND SHOULD *BE BROKEN ONLY AT THE SCORE.*

General:

Careful consideration of the various interacting drugs (including recently discontinued medications), physiologic conditions, and other factors such as smoking 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 IV**).

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 [eg, fever (see **CLINICAL PHARMACOLOGY,** *Fever*), 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; 8 to 12 hours after a UNI-DUR dose at steady state. For most patients, steady state will be reached after 4 days of dosing with UNI-DUR Tablets 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 (ie, 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 12 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 (eg, 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 6-12 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 10-20 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 μeq/L to 800 μeq/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 10-20 mcg/mL range may also transiently decrease serum concentrations of triiodothyronine (144 before, 131 after 1 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:

This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all adverse or intended effects.

The patient (or parent/caregiver) should be instructed to seek medical advice whenever nausea, vomiting, persistent headache, insomnia, restlessness, or rapid heartbeat 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 informed that theophylline interacts with a wide variety of drugs (see **Table II**). They 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.

UNI-DUR Tablets *should not be chewed or crushed.* Information relating to taking UNI-DUR Tablets in relation to meals or fasting should be provided.

Drug Interactions

Drug/Drug Interactions:

Theophylline interacts with a wide variety of drugs. The interaction may be pharmacodynamic, ie, 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, ie, 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 (eg, 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 (eg, 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 listing of drugs in **Table II** is 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 be required to achieve desired effect.
Alcohol	A single large dose of alcohol (eg, 3 mL/kg of whiskey) decreases theophylline clearance for up to 24 hours.	30% increase
Allopurinol	Decreases theophylline clearance at allopurinol doses ≥600 mg/day.	25% increase
Aminoglutethimide	Increases theophylline clearance by induction of microsomal enzyme activity.	25% decrease
Carbamazepine	Similar to aminoglutethimide.	30% decrease
Cimetidine	Decreases theophylline clearance by inhibiting cytochrome P450 1A2.	70% increase
Ciprofloxacin	Similar to cimetidine.	40% increase
Clarithromycin	Similar to erythromycin.	25% increase
Diazepam	Benzodiazepines increase CNS concentrations of adenosine, a potent CNS depressant, while theophylline blocks adenosine receptors.	Larger diazepam doses may be required to produce desired level of sedation. Discontinuation of theophylline without reduction of diazepam dose may result in respiratory depression.
Disulfiram	Decreases theophylline clearance by inhibiting hydroxylation 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 theophylline clearance by inhibiting cytochrome P450 3A3.	35% increase. Erythromycin steady-state serum concentrations decrease by a similar amount.
Estrogen	Estrogen-containing oral contraceptives decrease theophylline clearance in a dose-dependent fashion. The effect of progesterone on theophylline clearance is unknown.	30% increase
Flurazepam	Similar to diazepam.	Similar to diazepam.
Fluvoxamine	Similar to cimetidine.	Similar to cimetidine.
Halothane	Halothane sensitizes the myocardium to catecholamines; theophylline increases release of endogenous catecholamines.	Increased risk of ventricular arrhythmias.
Interferon, human recombinant alpha-A	Decreases theophylline clearance.	100% increase
Isoproterenol (IV)	Increases theophylline clearance.	20% decrease
Ketamine	Pharmacologic.	May lower theophylline seizure threshold.
Lithium	Theophylline increases renal lithium clearance.	Lithium dose required to achieve a therapeutic serum concentration increased 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 greater effect.
Mexiletine	Similar to disulfiram.	80% increase
Midazolam	Similar to diazepam.	Similar to diazepam.
Moricizine	Increases theophylline clearance.	25% decrease

SCHERING CORPORATION

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NDA SUPPL AMENDMENT
SL005/AL
FPL

April 2, 1997

Mr. Jerry Phillips, Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation & Research
MAN-II, Room 150
7500 Standish Place
Rockville, MD 20855

ANDA 89-822/S-005
ANDA 89-823/S-005
UNI-DUR (theophylline)
Extended-release Tablets

NOT the correct labeling see Lilia con 4-30-97 C-Holquist 4-30-97

SUBJECT: SUBMISSION OF FPL FOR PENDING SUPPLEMENT S-005

Dear Mr. Phillips:

We refer to our labeling supplement submitted on October 25, 1996 (S-005) which provided for the addition of a drug interaction precaution for ritonavir based on a literature report of a pharmacokinetic study. We also refer to your approvable letter dated February 18, 1997, which contained comments and requested that we submit FPL as an amendment to our pending supplement.

The purpose of this submission is to provide FPL revised per your February 18 approvable letter.

The enclosed FPL also includes labeling revisions that are the subject of pending supplement S-004 (dosing of UNI-DUR in the evening) and withdrawn supplement [redacted] Our recent submissions dated March 31, 1997 and April 1, 1997 explain the reason for withdrawing [redacted] and the [redacted].

Please be advised that Schering-Plough wishes to incorporate all of the labeling changes provided for in supplements [redacted], S-004, and S-005 into the next version of the package insert (i.e., "final" labeling) that will be implemented in commercial use. Therefore, we would greatly appreciate the concurrent approval of S-004 and S-005 so that we may implement the final labeling without delay.

Please be advised that the material and data contained in this submission are considered confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j), as well as the FDA regulations.

Sincerely,

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

MM:js
Enclosures

SCHERING CORPORATION

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FPL satisfactory
Catalgesic
4-30-97

April 1, 1997

AMENDMENT
SL004

Mr. Jerry Phillips, Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation & Research
MAN-II, Room 150
7500 Standish Place
Rockville, MD 20855

ANDA 89-822
ANDA 89-823
UNI-DUR (theophylline)
Extended-release Tablets

RECEIVED
APR 0 2 1997
GENERIC DRUGS

SUBJECT: SUBMISSION OF FPL

Dear Mr. Phillips:

We refer to our labeling supplements submitted on [redacted] and August 24, 1995 (S-004; dosing of UNI-DUR in the evening) which provided for revisions to the UNI-DUR package insert. We also refer to your approvable letters for these supplements dated [redacted] and November 25, 1995 (S-004) which contained comments on the labeling and requested that we submit FPL as amendments to each of these supplements.

We additionally refer to our letter dated [redacted] in which we requested withdrawal of [redacted] in order to permit the preparation and submission of one version of FPL to S-004 that includes both the [redacted] and evening dosing language.

The purpose of this submission is to provide FPL revised as requested in your approvable letters of December 6, 1996 and November 25, 1996. The enclosed FPL contains both the [redacted] and the evening dosing changes.

With regard to the class labeling changes, we adopted all of the comments contained in your December 6 approvable letter for [redacted] However, we felt that additional clarification was needed in order to place the [redacted]

In keeping with our desire to better differentiate the Uni-Dur pediatric information from the class labeling information, we have also slightly modified the Pediatric Use subsection of the insert to avoid any potential confusion regarding the pediatric age group in which Uni-Dur is approved for use. The revisions are illustrated below in redline and strikeout:

> Safety and effectiveness of UNI-DUR Extended-release Tablets in under 12 years of age have not been established. Other theophylline formulations, however, are safe and effective for the approved indications in pediatric patients under the age of 12. 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 IV).

We hope you agree that the clarifications outlined above remain consistent with the discussion and agreement during our October 1 meeting regarding the need to reconcile the general class labeling pediatric information with the pediatric information appropriate for our UNI-DUR extended-release product.

Please be advised that the material and data contained in this submission are considered confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j), as well as the FDA regulations.

Sincerely,

Mark J. Mariani for

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

MM:js
Enclosures

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

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 >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 >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, eg, diazepam, in increments of 0.1-0.2 mg/kg every 1-3 minutes until seizures are terminated. Repetitive seizures should be treated with a loading dose of phenobarbital (20 mg/kg infused over 30-60 minutes). Animal studies and case reports of theophylline overdose in humans 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, eg, patients with acute overdoses and serum theophylline concentrations >100 mcg/mL or chronic overdosage in patients >60 years of age with serum theophylline concentrations >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 (eg, transfer of a high-risk patient from one healthcare facility to another for extracorporeal removal) and clinical circumstances that significantly interfere with efforts to enhance theophylline clearance (eg, 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 (ie, markedly increases the LD_{50}). 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 1-2 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, 2-4 hours later, and then at sufficient intervals, eg, 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 (eg, 0.5 mg/kg up to 20 g, every 2 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 >20 <30 mcg/mL
1. Administer a single dose of oral activated charcoal.
2. Monitor the patient and obtain a serum theophylline concentration in 2-4 hours to ensure that the concentration is not increasing.

B. Serum Concentration >30 <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 2-4 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 >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 2-4 hours to gauge the effectiveness of therapy and to guide further treatment decisions.

Chronic Overdosage

A. Serum Concentration >20 <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 2-4 hours to ensure that the concentration is not increasing.

B. Serum Concentration >30 mcg/mL in patients <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 2-4 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 >30 mcg/mL in patients ≥ 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 2-4 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 5-10 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.

S 2 7 1

1165

UNI-DUR®
(theophylline)
Extended-release Tablets

Key Pharmaceuticals, Inc.
Kenilworth, NJ 07033 USA

Rev. 3/97

Table II. Clinically significant drug interactions with theophylline.* *(cont.)*

Drug	Type of Interaction	Effect**
Norfloxacin	Increases serum theophylline levels.	
Ofloxacin	Increases serum theophylline levels.	
Pancuronium	Theophylline may antagonize non-depolarizing neuromuscular blocking effects; possibly due to phospho-diesterase inhibition.	Larger dose of pancuronium may be required to achieve neuromuscular blockade.
Pentoxifylline	Decreases theophylline clearance.	30% increase
Phenobarbital (PB)	Similar to aminoglutethimide.	25% decrease after 2 weeks of concurrent PB.
Phenytoin	Phenytoin increases theophylline clearance by increasing microsomal enzyme activity. Theophylline decreases phenytoin absorption.	Serum theophylline *and* phenytoin concentrations decrease about 40%.
Propafenone	Decreases theophylline clearance and pharmacologic interaction.	40% increase. Beta$_2$-blocking effect may decrease efficacy of theophylline.
Propranolol	Similar to cimetidine and pharmacologic interaction.	100% increase. Beta$_2$-blocking effect may decrease efficacy of theophylline.
Rifampin	Increases theophylline clearance by increasing cytochrome P450 1A2 and 3A3 activity.	20%-40% decrease
Sucralfate	Reduced absorption of theophylline.	
Sulfinpyrazone	Increases theophylline clearance by increasing demethylation and hydroxylation. Decreases renal clearance of theophylline.	20% decrease
Tacrine	Similar to cimetidine, also increases renal clearance of theophylline.	90% increase
Thiabendazole	Decreases theophylline clearance.	190% increase
Ticlopidine	Decreases theophylline clearance.	60% increase
Troleandomycin	Similar to erythromycin.	33%-100% increase depending on troleandomycin 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.

Drug/Food Interactions:
The extent of theophylline absorption from UNI-DUR® Extended-release Tablets is similar when administered fasting or immediately after a high-fat content breakfast. However, the time to peak concentration was delayed following the high-fat content breakfast (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**). This breakfast contained 729 total kilocalories of which 55% were derived from 45 g of fat; and it consisted of two scrambled eggs, two strips of bacon, one slice of toast with 1 pat of butter, 3 oz. of hash brown potatoes, and 180 mL of whole milk. 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 (eg, cefazolin, cephalothin), however, may interfere with certain HPLC techniques. Caffeine and xanthine metabolites in 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 30-150 mg/kg) and rats (oral doses 5-75 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 B6C3F$_1$ mice at oral doses of 120, 270, and 500 mg/kg (approximately 1.0-3.0 times the human dose on a mg/m^2 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 B6C3F$_1$ mice at oral doses of 40-300 mg/kg (approximately 2.0 times the human dose on a mg/m^2 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 nonrodents (eg, 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 recommended human dose on a mg/m^2 basis or CD-1 rats at oral doses up to 260 mg/kg, approximately 3.0 times the recommended human dose on a mg/m^2 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 10-20 mcg/mL of theophylline a day is likely to receive 10-20 mg of theophylline per day. Serious adverse effects in the infant are unlikely unless the mother has toxic serum theophylline concentrations.

Pediatric Use:
Safety and effectiveness of UNI-DUR Extended-release Tablets in pediatric patients under 12 years of age have not been established. Other theophylline formulations, however, are safe and effective for the approved indications in pediatric patients under the age of 12. 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 IV**).

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 <10 mcg/mL (see **DOSAGE AND ADMINISTRATION**). Theophylline doses greater than 400 mg/day should be prescribed with caution in elderly patients.

ADVERSE REACTIONS

Adverse reactions associated with theophylline are generally mild when peak serum theophylline concentrations are <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 (eg, >300 mg/day in adults and >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 IV**). In a small percentage of patients (<3% of children and <10% of adults), the caffeine-like adverse effects persist during maintenance therapy, even at peak serum theophylline concentrations within the therapeutic range (ie, 10-20 mcg/mL). Dosage reduction may alleviate the caffeine-like adverse effects in these patients; however, persistent adverse effects should result in a re-evaluation of the need for continued theophylline therapy and the potential therapeutic benefit of alternative treatment.

Other adverse reactions that have been reported to occur at serum theophylline concentrations less than 20 mcg/mL include diarrhea, irritability, restlessness, fine skeletal muscle tremors, alopecia, muscle twitching/spasms, palpitations, rash, reflex hyperexcitability, transient diuresis, and ventricular arrhythmias. Whether or not theophylline caused these reported events is not known. In patients with hypoxia secondary to COPD, multifocal atrial tachycardia and flutter have been reported at serum theophylline concentrations ≥ 15 mcg/mL. There have been a few isolated reports of seizures at serum theophylline concentrations <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 <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 <20 mcg/mL have generally been milder than seizures associated with excessive serum theophylline concentrations resulting from an overdose (ie, they have generally been transient, often stopped without anticonvulsant therapy, and did not result in neurological residua).

Table III. Manifestations of theophylline toxicity.*

Sign/Symptom	Acute Overdose (Large Single Ingestion) Study 1 (n=157)	Acute Overdose (Large Single Ingestion) Study 2 (n=14)	Chronic Overdosage (Multiple Excessive Doses) Study 1 (n=92)	Chronic Overdosage (Multiple Excessive Doses) Study 2 (n=102)
Asymptomatic	NR**	0	NR**	6
Gastrointestinal				
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 with hemodynamic instability	7	14	40	0
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 >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 >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 (eg, 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,* ie, ingestion of a single large excessive dose (>10 mg/kg) as occurs in the context of an attempted suicide or isolated medication error, and (2) *chronic overdosage,* ie, 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 caregiver 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 20-30 mcg/mL range and 3% were >30 mcg/mL. Approximately two thirds of the patients with serum theophylline concentrations in the 20-30 mcg/mL range had one or more manifestations of toxicity while >90% of patients with serum theophylline concentrations >30 mcg/mL were clinically intoxicated. Similarly, in other reports, serious toxicity from theophylline is seen principally at serum concentrations >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 >100 mcg/mL. After a chronic overdosage, generalized seizures, life-threatening cardiac arrhythmias, and death may occur at serum theophylline concentrations >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 >60 years are at the greatest risk for severe toxicity and mortality after a chronic overdosage. Pre-existing or concurrent disease may also significantly increase the susceptibility of a patient to a particular toxic manifestation, eg, 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.

DOSAGE AND ADMINISTRATION

The extent of absorption of theophylline from UNI-DUR Tablets when administered fasting or immediately after a high-fat content breakfast is similar. However, the time to peak concentration is delayed (see **PRECAUTIONS, Drug/Food Interactions**).

Effective use of theophylline (ie, the concentration of drug in the serum associated with optimal benefit and minimal risk of toxicity) is considered to occur when the theophylline concentration is maintained from 10 to 15 mcg/mL.

Patients who clear theophylline normally or relatively slowly, eg, nonsmokers, may be reasonable candidates for taking UNI-DUR Tablets once daily. However, certain patients, such as the young, smokers, and some nonsmoking adults are likely to metabolize theophylline more rapidly and may require dosing at 12-hour intervals. Such patients may experience symptoms of bronchospasm toward the end of a once-daily dosing interval and/or require a higher daily dose (higher than those recommended in labeling) and are more likely to experience relatively wide peak to trough differences in serum theophylline concentrations.

UNI-DUR Tablets may be administered either in the morning or in the evening.

UNI-DUR Tablets *should not be chewed or crushed.*

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 10-20 mcg/mL range varies fourfold among otherwise similar patients in the absence of factors known to alter theophylline clearance (eg, 400-1600 mg/day in adults <60 years old and 10-36 mg/kg/day in children 1-9 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/day in adults <60 years or 22 mg/kg/day in children 1-9 years, the steady-state peak serum theophylline concentration will be <10 mcg/mL in about 30% of patients, 10-20 mcg/mL in about 50%, and 20-30 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 IV**). 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, Monitoring Serum Theophylline Concentrations,** and **DOSAGE AND ADMINISTRATION, Table V**). Healthcare providers should instruct patients and caregivers 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, eg, every 24 hours.

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

Table IV contains theophylline dosing titration schema recommended for patients in various age groups and clinical circumstances. **Table V** 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 dose adjustments in order to decrease the risk of potentially serious adverse events associated with unexpected large increases in serum theophylline concentration.**

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

A. Children (12-15 years) and adults (16-60 years) without risk factors for impaired clearance.

Titration Step	*Children <45 kg*	*Children >45 kg and adults*
1. Starting dose	12-14 mg/kg/day up to a maximum of 300 mg/day administered QD*	300-400 mg/day[1] administered QD*
2. After 3 days, *if tolerated*, increase dose to:	16 mg/kg/day up to a maximum of 400 mg/day administered QD*	400-600 mg/day[1] administered QD*
3. After 3 more days, *if tolerated*, increase dose to:	20 mg/kg/day up to a maximum of 600 mg/day administered QD*	As with all theophylline products, doses greater than 600 mg should be titrated according to blood level (see **Table V**).

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B. **Patients With Risk Factors For Impaired Clearance, The Elderly (>60 Years), And Those In Whom It Is Not Feasible To Monitor Serum Theophylline Concentrations:**

In children 12-15 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 ≥16 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 12 hours) to prevent breakthrough symptoms resulting from low trough concentrations before the next dose.

[1]If caffeine-like adverse effects occur, then consideration should be given to a lower dose and titrating the dose more slowly (see **ADVERSE REACTIONS**).

Table V. Dosage adjustment guided by serum theophylline concentration.

Peak Serum Concentration	Dosage Adjustment
<9.9 mcg/mL	If symptoms are not controlled and current dosage is tolerated, increase dose about 25%. Recheck serum concentration after 3 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- to 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.¶
20-24.9 mcg/mL	Decrease dose by 25% even if no adverse 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).
>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 (eg, sustained fever), or a drug that interacts with theophylline is added or discontinued (see **WARNINGS**).

HOW SUPPLIED

UNI-DUR Extended-release Tablets are supplied as controlled-release tablets containing either 400 mg or 600 mg of theophylline anhydrous. They are mottled white, capsule-shaped tablets; scored on one side and debossed with the product name and strength on the other.

UNI-DUR Extended-release Tablets 400 mg are available in bottles of 100's (NDC 0085-0694-01).

UNI-DUR Extended-release Tablets 600 mg are available in bottles of 100's (NDC 0085-0814-01).

STORAGE CONDITIONS

Keep bottles tightly closed. Store between 15° and 25°C (59° and 77°F).

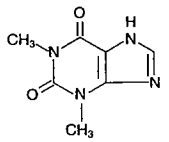
CAUTION: Federal law prohibits dispensing without prescription.

Some of the information contained in this insert (eg, information regarding pediatric patients under the age of 12) was derived from FDA's Class Labeling Guidance for Immediate-Release Theophylline Products and is intended for informational purposes only.

DESCRIPTION

UNI-DUR® Extended-release Tablets for oral administration contain 400 or 600 mg anhydrous theophylline in an extended-release system which allows a 24-hour dosing interval for appropriate patients.

Theophylline is a bronchodilator, structurally classified as a methylxanthine. It occurs as a white, odorless, crystalline powder with a bitter taste. Anhydrous theophylline has the chemical name 1*H*-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 $C_7H_8N_4O_2$ with a molecular weight of 180.17.

The inactive ingredients for UNI-DUR 400 and 600 mg Extended-release Tablets include: acacia, NF; acetone; cellulose acetate phthalate, NF; cetyl alcohol, NF; confectioner's sugar, NF; corn starch, NF; diethyl phthalate, NF; glyceryl monostearate; lactose monohydrate, NF; magnesium stearate, NF; myristyl alcohol, NF; nonpareil seeds (sugar spheres), NF; and white wax, NF.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Theophylline has two distinct actions in the airways of patients with reversible obstruction; smooth muscle relaxation (ie, bronchodilation) and suppression of the response of the airways to stimuli (ie, non-bronchodilator prophylactic effects). While the mechanisms of action of theophylline are not known with certainty, studies in animals suggest that bronchodilation is mediated by the inhibition of two isozymes of phosphodiesterase (PDE III 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 (eg, hypotension, tachycardia, headache, and emesis) and adenosine receptor antagonism (eg, 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 >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 coadministration 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 (eg, at 24-hour intervals) and periodically in patients receiving long-term therapy (eg, 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, Monitoring Serum Theophylline Concentrations** and **DOSAGE AND ADMINISTRATION**).

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)
Age		
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 3-30 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 nonsmoking asthmatics	0.65 (0.27-1.03)	8.7 (6.1-12.8)
Elderly (>60 years)		
nonsmokers 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 nonsmoker >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)

¶ 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 1 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 nonlinear pharmacokinetics.

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

UNI-DUR Pharmacokinetics

Following the single-dose crossover administration of a 600 mg UNI-DUR Tablet to 20 healthy male subjects after an overnight fast, a peak serum theophylline concentration of 5.3 ± 1.3 mcg/mL was obtained at 13.6 ± 3.7 hours and the mean area under the curve extrapolated to infinity (AUC_{inf}) was 132.7 ± 45.1 mcg hr/mL. When taken immediately after a high-fat breakfast, the mean AUC_{inf} was 136.0 ± 36.7 mcg hr/mL with a mean peak theophylline serum level of 5.2 ± 1.5 mcg/mL at 17.1 ± 6.3 hours. While food did not affect the extent of absorption as evidenced by the similar AUC_{inf} values, food did prolong the time to peak concentration. The absorption from half tablets of the 600 mg product was also evaluated and found to be bioequivalent to that of the whole tablets. The relative extent of absorption of theophylline from the 600 mg UNI-DUR Tablet, fasting, when compared to an immediate-release theophylline tablet, was 84.3%; and for the nonfasting treatment was 88.7%.

In a separate multiple-dose study, two 400 mg UNI-DUR Tablets were compared to one 600 mg UNI-DUR Tablet. This study was a two-way, randomized, crossover multiple-dose study in 17 nonsmoking healthy males. Both products were dosed once a day in the morning after an overnight fast and 1 hour prior to a meal for 5 days. There was no significant difference in any of the pharmacokinetic parameters when corrected for dose.

The mean dose AUC_{ss} (corrected to the 600 mg dose) for the two 400 mg UNI-DUR Tablets was 179.7 ± 62.9 mcg hr/mL and for the 600 mg UNI-DUR Tablet was 170.9 ± 75.2 mcg hr/mL. The two 400 mg UNI-DUR Tablets reached dose corrected maximum serum concentration of 9.8 ± 2.6 mcg/mL and the 600 mg UNI-DUR Tablet reached a maximum of 9.7 ± 3.5 mcg/mL. The minimum concentrations were 4.9 ± 2.6 mcg/mL and 4.4 ± 2.6 mcg/mL for the two 400 mg and 600 mg UNI-DUR Tablets, respectively.

Steady-state pharmacokinetics were determined in a multiple-dose, crossover study with 24 healthy nonsmoking male subjects having an average theophylline clearance of 5.70 ± 2.36 (S.D.) liters per hour. Following an overnight fast, a UNI-DUR 600 mg Extended-release Tablet was administered once daily in the morning for 5 consecutive days. The UNI-DUR Tablet exhibited better extended-release characteristics compared with a reference extended-release q12h product (2 x 300 mg) administered once daily in the morning following an overnight fast for 5 consecutive days. The results are noted as follows (mean values ± S.D.):

	AUC_{ss} (mcg hr/mL)	C_{max} (mcg/mL)	C_{min} (mcg/mL)	T_{max} (hr)
UNI-DUR	119 ± 36	6.9 ± 2.4	3.7 ± 1.3	11.5 ± 5.7
Reference	154 ± 37	10.5 ± 2.3	2.5 ± 1.1	7.6 ± 1.7

The mean percent fluctuation [$(C_{max}-C_{min}/C_{min})$ x 100] was 130% for the once-daily UNI-DUR regimen and 389% for the reference q12h product administered once daily. The extent of theophylline absorption from UNI-DUR Tablets relative to the reference q12h product was 74.9% (95% C.I. = 67-84).

In a randomized, multiple-dose crossover study with 18 healthy male subjects, a 600 mg UNI-DUR Extended-release Tablet was administered once daily either in the morning or evening for 5 consecutive days. The theophylline AUC_{ss} for the 24-hour period following the dose given on day 5 was equivalent for morning (177 ± 89 mcg hr/mL) and evening (175 ± 76 mcg hr/mL) administration. The peak theophylline concentrations (C_{max}) at steady state were also equivalent for morning (10.6 ± 4.9 mcg/mL) and evening (10.3 ± 4.0 mcg/mL) administration.

Steady-state pharmacokinetics comparing UNI-DUR Tablets once-daily administration with twice-daily administration were determined in a multiple-dose, crossover study with 24 healthy, nonsmoking male subjects having an average theophylline clearance of 4.53 ± 1.21 (S.D.) liters per hour. Using UNI-DUR 400 mg Extended-release Tablets, a total daily theophylline dose of 800 mg was administered for 5 consecutive days either once daily as two tablets in the morning (8 AM) with a standardized breakfast or twice daily as one tablet in the morning (8 AM) with a standardized breakfast or twice daily as one tablet in the morning (8 AM) with a standardized breakfast and one tablet in the evening (8 PM). The once-daily UNI-DUR regimen was bioequivalent to the twice-daily UNI-DUR regimen. The results are noted as follows (mean values ± S.D.):

	AUC_{ss} (mcg hr/mL)	C_{max} (mcg/mL)	C_{min} (mcg/mL)	T_{max} (hr)
QD Regimen	187 ± 45	10.4 ± 2.9	6.0 ± 1.3	12.0 ± 3.7
q12h Regimen	187 ± 43	9.4 ± 2.2	8.4 ± 2.6	14.5 ± 6.6

The mean percent fluctuation [$(C_{max}-C_{min}/C_{min})$ x 100] was 78% for the once-daily UNI-DUR regimen and 17% for the twice-daily UNI-DUR regimen. The extent of theophylline absorption from the once-daily UNI-DUR regimen relative to the twice-daily UNI-DUR regimen was 100% (95% C.I. = 95-105).

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 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 (10-20 mcg/mL) due to elevated concentrations of the pharmacologically active unbound drug. Similarly, a patient with decreased theophylline binding may have a subtherapeutic 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 1 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 P450 1A2, while cytochromes P450 2E1 and P450 3A3 catalyze the hydroxylation to 1,3-dimethyluric acid. Demethylation to 1-methylxanthine appears to be catalyzed either by cytochrome P450 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 1 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 N-demethylation and hydroxylation pathways of theophylline biotransformation are capacity-limited. Due to the wide intersubject variability of the rate of theophylline metabolism, nonlinearity of elimination may begin in some patients at serum theophylline concentrations <10 mcg/mL. Since this nonlinearity 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 V**). Accurate prediction of dose-dependency of theophylline metabolism in patients *a priori* is not possible, but patients with very high initial clearance rates (ie, 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 3 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 (ie, 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, 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 immediate-release theophylline, steady state is reached in 30-65 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 4-5 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 (8-12 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 (>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 1 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 3 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, eg, about 10%, of the administered theophylline dose is excreted unchanged in the urine of children greater than 3 months of age and adults. Since little theophylline is excreted unchanged in the urine and since active metabolites of theophylline (ie, 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 (eg, 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 appear 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 1 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 or lesser temperature elevations for longer periods, are probably required to produce a clinically significant increase in serum theophylline concentrations. Children with rapid rates of theophylline clearance (ie, those who require a dose that is substantially larger than average [eg, >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
UNI-DUR Extended-release Tablets are indicated for the treatment of the symptoms and reversible airflow obstruction associated with chronic asthma and other chronic lung diseases, eg, emphysema and chronic bronchitis.

CONTRAINDICATIONS
UNI-DUR Extended-release Tablets are contraindicated in patients with a history of hypersensitivity to theophylline or other components in the product.

WARNINGS
Serious side effects such as ventricular arrhythmias, convulsions, or even death may appear as the first sign of toxicity without any recognized prior warnings. Less serious signs of theophylline toxicity (eg, nausea and restlessness) may occur frequently when initiating therapy but are usually transient. When such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 mcg/mL. Stated differently, serious toxicity is not reliably preceded by less severe side effects.

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 (peptic ulcer disease should be controlled with appropriate therapy since theophylline is known to increase peptic acid secretion)
- 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 so as to lower serum theophylline levels to within the therapeutic range 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°F 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 (eg, cimetidine, erythromycin, tacrine) or stopping a concurrently administered drug that enhances theophylline metabolism (eg, 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 should be 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, Dosage Guidelines, Table V**).

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 beta$_2$-selective agonists and systemically administered corticosteroids 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, Monitoring Serum Theophylline Concentrations**).

As the rate of theophylline clearance may be dose-dependent (ie, steady-state serum concentrations may increase disproportionately to the increase in dose), an increase in dose based upon a subtherapeutic 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 V**).

PRECAUTIONS
UNI-DUR TABLETS SHOULD *NOT* BE CHEWED OR CRUSHED AND SHOULD *BE BROKEN ONLY AT THE SCORE.*

General:
Careful consideration of the various interacting drugs (including recently discontinued medications), physiologic conditions, and other factors such as smoking 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 IV**).

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 [eg, fever (see **CLINICAL PHARMACOLOGY,** *Fever*), 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; 8 to 12 hours after a UNI-DUR dose at steady state. For most patients, steady state will be reached after 4 days of dosing with UNI-DUR Tablets 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 (ie, 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 12 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 (eg, 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 6-12 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 10-20 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 μeq/L to 800 μeq/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

WARNINGS

Serious side effects such as ventricular arrhythmias, convulsions, or even death may appear as the first sign of toxicity without any recognized prior warnings. Less serious signs of theophylline toxicity (eg, nausea and restlessness) may occur frequently when initiating therapy but are usually transient. When such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 mcg/mL. Stated differently, serious toxicity is not reliably preceded by less severe side effects.

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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 (peptic ulcer disease should be controlled with appropriate therapy since theophylline is known to increase peptic acid secretion)
Seizure disorders
Cardiac arrhythmias (not including bradyarrhythmias)

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There are several readily identifiable causes of reduced theophylline clearance. ***If the total daily dose is not appropriately reduced so as to lower serum theophylline levels to within the therapeutic range 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°F 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 (eg, cimetidine, erythromycin, tacrine) or stopping a concurrently administered drug that enhances theophylline metabolism (eg, carbamazepine, rifampin). (See **PRECAUTIONS, Drug Interactions, Table II.**)

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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 should be 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, Dosage Guidelines, Table V**).

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 beta$_2$-selective agonists and systemically administered corticosteroids 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, Monitoring Serum Theophylline Concentrations**).

As the rate of theophylline clearance may be dose-dependent (ie, steady-state serum concentrations may increase disproportionately to the increase in dose), an increase in dose based upon a subtherapeutic 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 V**).

PRECAUTIONS

UNI-DUR TABLETS SHOULD *NOT* BE CHEWED OR CRUSHED AND SHOULD *BE BROKEN ONLY AT THE SCORE.*

General:

Careful consideration of the various interacting drugs (including recently discontinued medications), physiologic conditions, and other factors such as smoking 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 IV**).

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 [eg, fever (see **CLINICAL PHARMACOLOGY, *Fever***), 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; 8 to 12 hours after a UNI-DUR dose at steady state. For most patients, steady state will be reached after 4 days of dosing with UNI-DUR Tablets 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 (ie, 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 12 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 (eg, 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 6-12 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 10-20 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 μeq/L to 800 μeq/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 10-20 mcg/mL range may also transiently decrease serum concentrations of triiodothyronine (144 before, 131 after 1 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:

This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all adverse or intended effects.

The patient (or parent/caregiver) should be instructed to seek medical advice whenever nausea, vomiting, persistent headache, insomnia, restlessness, or rapid heartbeat 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 informed that theophylline interacts with a wide variety of drugs (see **Table II**). They 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.

UNI-DUR Tablets *should not be chewed or crushed.* Information relating to taking UNI-DUR Tablets in relation to meals or fasting should be provided.

Drug Interactions

Drug/Drug Interactions:

Theophylline interacts with a wide variety of drugs. The interaction may be pharmacodynamic, ie, 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, ie, 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 (eg, 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 (eg, 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 listing of drugs in **Table II** is 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 be required to achieve desired effect.
Alcohol	A single large dose of alcohol (eg, 3 mL/kg of whiskey) decreases theophylline clearance for up to 24 hours.	30% increase
Allopurinol	Decreases theophylline clearance at allopurinol doses ≥600 mg/day.	25% increase
Aminoglutethimide	Increases theophylline clearance by induction of microsomal enzyme activity.	25% decrease
Carbamazepine	Similar to aminoglutethimide.	30% decrease
Cimetidine	Decreases theophylline clearance by inhibiting cytochrome P450 1A2.	70% increase
Ciprofloxacin	Similar to cimetidine.	40% increase
Clarithromycin	Similar to erythromycin.	25% increase
Diazepam	Benzodiazepines increase CNS concentrations of adenosine, a potent CNS depressant, while theophylline blocks adenosine receptors.	Larger diazepam doses may be required to produce desired level of sedation. Discontinuation of theophylline without reduction of diazepam dose may result in respiratory depression.
Disulfiram	Decreases theophylline clearance by inhibiting hydroxylation 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 theophylline clearance by inhibiting cytochrome P450 3A3.	35% increase. Erythromycin steady-state serum concentrations decrease by a similar amount.
Estrogen	Estrogen-containing oral contraceptives decrease theophylline clearance in a dose-dependent fashion. The effect of progesterone on theophylline clearance is unknown.	30% increase
Flurazepam	Similar to diazepam.	Similar to diazepam.
Fluvoxamine	Similar to cimetidine.	Similar to cimetidine.
Halothane	Halothane sensitizes the myocardium to catecholamines; theophylline increases release of endogenous catecholamines.	Increased risk of ventricular arrhythmias.
Interferon, human recombinant alpha-A	Decreases theophylline clearance.	100% increase
Isoproterenol (IV)	Increases theophylline clearance.	20% decrease
Ketamine	Pharmacologic.	May lower theophylline seizure threshold.
Lithium	Theophylline increases renal lithium clearance.	Lithium dose required to achieve a therapeutic serum concentration increased 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 greater effect.
Mexiletine	Similar to disulfiram.	80% increase
Midazolam	Similar to diazepam.	Similar to diazepam.
Moricizine	Increases theophylline clearance.	25% decrease

ANDA 89-822/S-004 (400 mg)
89-823/S-004 (600 mg)

Schering Corporation
Attention: Richard N. Spivey
2000 Galloping Hill Road
Kenilworth, NJ 07033

NOV 25 1996

Dear Sir:

This is in reference to your supplemental new drug applications dated August 24, 1995, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug applications for Uni-Dur® (Theophylline Extended-release Tablets).

The supplemental applications provide for revised package insert labeling to include evening dosing with Uni-Dur® tablets.

The proposed labeling revisions and supporting data were forwarded to the Division of Bioequivalence (HFD-650) and the Division of Pulmonary Drug Products (HFD-570) for their review and comment. Upon completion of their review of these supplemental applications they are approvable.

The *in vivo* multiple dose pharmacokinetic study (#C87-009) conducted comparing the steady state performance of Uni-Dur® 1 x 600 mg tablet following AM (morning) and PM (evening) dosing has been found to be acceptable to the Division of Bioequivalence. The results of this study demonstrate that, based on the rate and extent of absorption, the PM dosing regimen of Uni-Dur® 1 x 600 mg tablets is bioequivalent to its AM dosing regimen. However, the information submitted in the controlled studies, S87-056 and I88-201, are not adequate to support the labeling claim "Uni-Dur administered once-a-day in the evening has been shown to maintain pulmonary function similar to theophylline twice a day with no increase in the incidence of adverse events" for the following reason:

Uni-Dur® dosed once-daily in the evening proved to be clearly less well tolerated in these trials than Theo-Dur® BID, to a statistically significant degree in study S87-056. Though these resultant adverse events did not appear to be often times severe nor serious in nature, they were clearly indicative that patients did not tolerate this switch in therapy as well as the claims in the labeling.

Therefore, before the supplemental applications may be approved, it is necessary that you revise as follows:

a. CLINICAL PHARMACOLOGY

UNI-DUR Pharmacokinetics - Delete the following sentence:

[ ]

b. The insert must be revised to be in accord with the revisions outlined in supplement 003.

Prepare and submit final printed labeling as amendments to these supplemental applications.

The changes provided for in these supplemental applications may not be initiated until you have been notified in writing that the supplemental applications are approved.

Sincerely yours,

Jerry Phillips 11/23/96

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 89-822/S-004
89-823/S-004
Division File
HFD-600/Reading File
HFD-613/CHolquist/CHoppes/JGrace(no cc:)
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Approvable Letter - Multiple Supplements

CHolquist 11/21/96 CHoppes 11/22/96

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Page(s) of trade secret and /or confidential commercial information

BIOAVAILABILITY

Schering-Plough
Research Institute

2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530
Telephone (908) 298-4000
Telex 6853298 SP KEN

NDA NO. 89822 REF. NO. SL-014

NDA SUPPL FOR Labeling Revision/Draft Labeling

August 24, 1995

Charles Ganley, M.D.,Acting Director
Office of Generic Drugs
Center for Drug Evaluation & Research
MPN-II, Room 150
7500 Standish Place
Rockville, MD 20855

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AUG 25 1995
GENERIC DRUGS

ANDA 89-822
89-823
Uni-Dur (theophylline)
Extended-release
Tablets

SUBJECT: Labeling Supplement - Revised Package Insert

Dear Dr. Ganley:

We are submitting a supplement seeking approval to include dosing in the evening in the labeling for Uni-Dur (theophylline) Extended-release 400 mg (ANDA 89-822) and 600 mg (ANDA 89-823) Tablets.

We are submitting this supplement to ANDA 89-822 and will cross-reference it to ANDA 89-823.

The clinical program to support this evening dosing claim consists of two controlled clinical safety and efficacy studies in 221 patients with reversible airway obstruction, predominantly patients with asthma. Three uncontrolled studies with 428 patients are also included to show that patients taking twice daily theophylline products can be safely and effectively converted to Uni-Dur once daily dosed in the evening. A clinical pharmacology study in 18 healthy adult male subjects comparing the Pharmacokinetic profile of Uni-Dur dosed once daily in the evening to Uni-Dur dosed once daily in the morning is offered in support of the clinical studies.

The package insert submitted with this supplement reflects the theophylline class labeling guidelines issued in February 1995. The revisions specific to this supplement have been "redlined" to ease your review.

In accordance with Section 306(k) of the FD&C Act, Schering Corporation certifies that, with respect to this application, it did not and will not knowingly use the services of any persons that have been debarred under the provisions of Section 306(a) or (b) of the Act.

5 Sep 95

Please be advised that the material and data contained in this submission are considered confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j), as well as the FDA regulations.

Sincerely,

Paula E. Rhelda

for/Richard N. Spivey, Pharm.D., Ph.D.
Senior Director
U.S. Regulatory Affairs

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BIOAVAILABILITY

Schering-Plough
Research Institute

2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530
Telephone (908) 298-4000
Telex 6853298 SP KEN

DESK COPY

March 20, 1995

Douglas Sporn, Acting Director
Office of Generic Drugs
Center for Drug Evaluation & Research
MPN-II, Room 150
7500 Standish Place
Rockville, MD 20855

ANDA 89-822 ✓
89-823
UNI-DUR (theophylline)
Extended-release Tablets

SC-002

NDA NO. REF. NO.
NDA SUPPL FOR Control Rev.

Subject: Response to FDA Request

Dear Mr. Sporn:

As requested in the March 10, 1995 telephone conversation with Dr. Alexander Giaquinto, we are providing the following additional information to support our proposed dissolution specifications for Uni-Dur Extended-release Tablets:

- Tablet dissolution stability data on 12 production scale batches of Uni-Dur 400 mg and 600 mg Tablets manufactured between 1990 and 1993 (Attachment 1). These data have not previously been submitted.

- Study report to K89-440-01: Multiple Dose Pharmacokinetics of Theophylline from Two Different Lots of Uni-Dur 600 mg Tablets Dosed Once Daily in the Morning. This information, originally submitted October 18, 1990, describes the pharmacokinetics of "aged" versus "fresh" product (Attachment 2).

Please be advised that the material and data contained in this submission are considered confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j), as well as the FDA regulations.

Sincerely,

Richard N. Spivey, PharmD., Ph.D.
Senior Director
Worldwide Regulatory Affairs

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ORIGIN

NDA NO. ______ REF. NO. SL-001

NDA SUPPL FOR Label Rev

Key Pharmaceuticals

Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033
Telephone (201) 298-4000
Mail To: P.O. Box 525
Kenilworth, N.J. 07033

January 18, 1995

Mr. Douglas Sporn, Acting Director
Office of Generic Drugs
Center for Drug Evaluation & Research
MPN-II, Room 150
7500 Standish Place
Rockville, Maryland 20855

ANDA 89-822
89-823
Uni-Dur (theophylline)
Extended-release Tablets

Subject: Special Supplement: Changes Being Effected

Dear Mr. Sporn:

We are submitting a Special Supplement: Changes Being Effected in order to add norfloxacin and sucralfate to the Drug/Drug Interactions section of the package insert (PI) used for Uni-Dur Extended-release Tablets. These interactions with theophylline appear in the labeling for both norfloxacin and sucralfate. In addition, norfloxacin appears in the Drug Interactions section of the UNIPHYL® labeling. For your convenience, we are including copies of the norfloxacin, sucralfate and UNIPHYL® labeling.

This revision to the PI will be implemented when Uni-Dur is first introduced to the market.

Please be advised that the material and data contained in this submission are considered confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j), as well as the FDA regulations.

Sincerely,

Richard N. Spivey, Pharm.D., Ph.D.
Senior Director
U.S. Regulatory Affairs

RNS:lt
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