DRUG MARKET WITHDRAWAL

THEOPHYLLINE EXTENDED-RELEASE TABLETS USP 400mg
100s Container pack (Tablets)
(NDC 68462-380-01)
(Glenmark)

August 8, 2025

Dear Pharmacy, Wholesale and Retail Customer:

This is to inform you that Glenmark is initiating a Market Withdrawal at the Retail level involving the following prescription product:

Theophylline Extended-Release Tablets USP 400 mg (100's Tablets)

Sr. No.	NDC Code	Batch No.	Pack Size	Exp. Date
1	68462-380-01	19233993	100's Tablets	Sep-2025
2	68462-380-01	19234027	100's Tablets	Sep-2025
3	68462-380-01	19234047	100's Tablets	Sep-2025
4	68462-380-01	19234070	100's Tablets	Sep-2025
5	68462-380-01	19234079	100's Tablets	Sep-2025
6	68462-380-01	19234093	100's Tablets	Sep-2025
7	68462-380-01	19234114	100's Tablets	Sep-2025
8	68462-380-01	19234385	100's Tablets	Oct-2025
9	68462-380-01	19234427	100's Tablets	Oct-2025
10	68462-380-01	19234459	100's Tablets	Oct-2025
11	68462-380-01	19234462	100's Tablets	Oct-2025
12	68462-380-01	19240385	100's Tablets	Dec-2025
13	68462-380-01	19240437	100's Tablets	Jan-2026
14	68462-380-01	19241185	100's Tablets	Feb-2026
15	68462-380-01	19241197	100's Tablets	Feb-2026
16	68462-380-01	19241220	100's Tablets	Feb-2026
17	68462-380-01	19241238	100's Tablets	Feb-2026
18	68462-380-01	19244538	100's Tablets	Oct-2026
19	68462-380-01	19250174	100's Tablets	Dec-2026

Glenmark Pharmaceuticals Inc. USA 750 Corporate Drive, Mahwah, NJ 07430
T: 1 201 684 8000 F: 1 201 831 0080 www.glenmarkpharma.com/usa

Glenmark is initiating a market withdrawal at the ***Retail level*** for the above-identified batches of Theophylline Extended-Release Tablets 400 mg due to failure results were reported for the Dissolution (By UV) test for commercial annual stability batch #19230553 of Theophylline Extended-Release Tablets 400mg at the long-term (25°C/60% RH) shelf life stability interval. The batch already expired in January 2025; hence no market action is warranted.

As part of impact assessment testing, Theophylline Extended-Release Tablets 400mg batches within the shelf life were tested for dissolution. During this testing, failure results are reported in 8 out of 27 batches of Theophylline Extended-Release Tablets 400mg. A voluntary recall is being initiated for these eight (8) batches that are within shelf life.

As an abundance of caution, Glenmark is initiating market withdrawal of the remaining above mentioned 19 batches of Theophylline Extended-Release Tablets 400mg that are within shelf life wherein the Dissolution test results are complying with the Dissolution specification criteria when tested as part of impact assessment.

To date, Glenmark has not received any reports of adverse events related to this market withdrawal. The Health hazard assessment (HHA) concluded that the observed OOS results in dissolution testing for the concerned batches of Theophylline Extended-Release Tablets 400mg are not expected to pose a clinically significant risk to patient health and safety.

Please see the details of product batches listed in the above table and refer to the enclosed product labels for ease in identifying the product.

Please examine your inventory, and if you have any inventory available for the batches specified in the above table, you should quarantine such product immediately and not dispense any further product from these lots. Glenmark Pharmaceuticals Inc., USA initiated shipment of this product on 11/22/2023.

In addition, if you are a wholesaler/ distributor, who has further distributed this product, please identify those retail customers and notify them at once of this market withdrawal. Your notification to your retail customers may be enhanced by including a copy of this market withdrawal notification letter. Again, this market withdrawal should be carried out to the retail level only. Because this is not a consumer level market withdrawal, notice to the consumer level is not required.

Glenmark is requesting the batches specified in the above table to be returned to Inmar Rx Solutions (address below) using the Postage Paid Product Return label that was provided in your Market Withdrawal Return Packet.

Glenmark Pharmaceuticals Inc. USA 750 Corporate Drive, Mahwah, NJ 07430
T: 1 201 684 8000 F: 1 201 831 0080 www.glenmarkpharma.com/usa

Inmar Rx Solutions
3845 Grand Lakes Way
Grand Prairie, TX 75050

Please complete and return the enclosed response form preferably within 72 hours of receipt of this notification. Please either fax your response to 817-868-5362 or email to Rxrecalls@Inmar.com.

If you have any questions regarding your market withdrawal return please contact Inmar at **(877) 560-6078**

Inmar office hours are Monday through Friday, from 9 am to 5 pm EST.

This market withdrawal is being made with the knowledge of the Food and Drug Administration.

Thank you for your cooperation,

Sincerely,

GLENMARK PHARMACEUTICALS INC., USA

thomas.callaghan@glenmarkpharma.com
Digitally signed by thomas.callaghan@glenmarkpharma.com
Date: 2025.08.08 08:41:43 -04'00'

Thomas Callaghan

Executive Director - Regulatory Affairs, North America

US Agent for Glenmark Pharmaceuticals Limited

Enclosure(s):

Product Labels

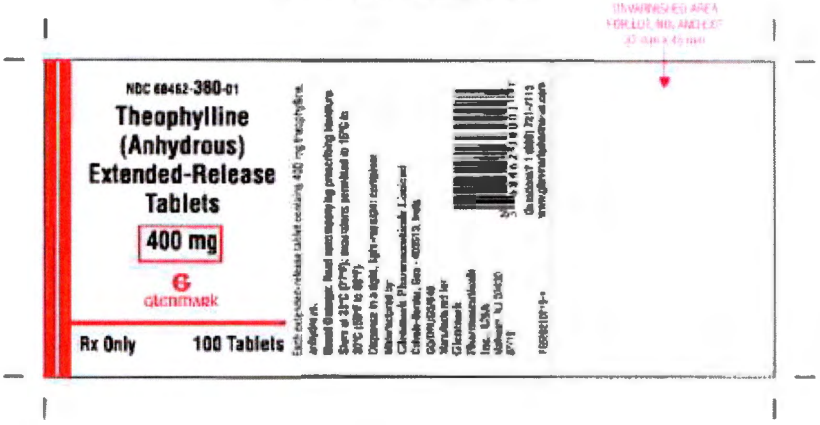
Market Withdrawal Return Response Form

Glenmark Pharmaceuticals Inc. USA 750 Corporate Drive, Mahwah, NJ 07430
T: 1 201 684 8000 F: 1 201 831 0080 www.glenmarkpharma.com/usa

Product label:

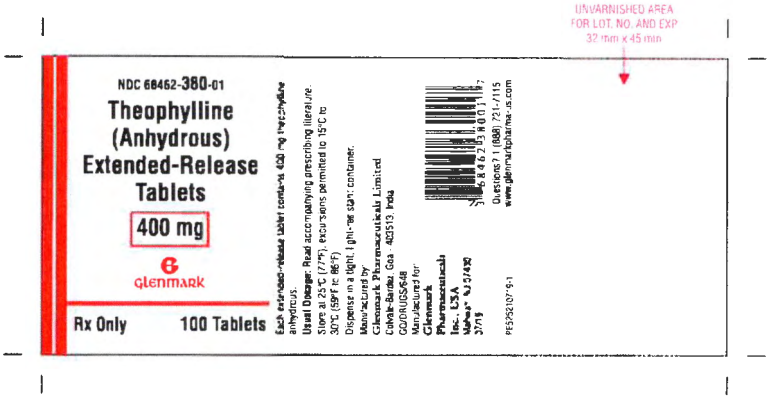
Theophylline Extended-Release Tablets 400 mg (100's Tablets)

JAR SIZE : 100 CC
SAME SIZE ARTWORK
LABEL SIZE : 105 mm x 46 mm



Glenmark Pharmaceuticals Inc. USA 750 Corporate Drive, Mahwah, NJ 07430
T: 1 201 684 8000 F: 1 201 831 0080 www.glenmarkpharma.com/usa

JAR SIZE : 100 CC
SAME SIZE ARTWORK
LABEL SIZE : 105 mm x 45 mm



MINIMUM FONT SIZE: 4.5 pt

GLENMARK PHARMACEUTICALS LTD.			
PRODUCT NAME: THEOPHYLLINE E R TABLETS 400 MG	**DATE:**	**PANTONE SHADE NO:**	186 C BLACK
ITEM CODE: PE52521 **VERSION:** 0719-1	**PKG. DEV.:**	Item code Version Consistency of Design, overprint area, Pack size, Dimensions & Layout	
PHARMACODE:	**RA**	Regulatory Text	
COUNTRY: USA	**QA:**	Entire Text	
LOCATION: COLVALE - GOA	**PRODUCTION:**	Machine Suitability	
PACK : LABEL - 100 TABLETS	**REMARKS:**		
ACTUAL SIZE: 105 mm x 45 mm			
SPECIFICATION: A UV VARNISH COATED FASPRINT NG/PERMANENT (HITAC)/ PET 23 STICKER LABEL FROM AVERY DENISON PRINTED AS PER APPROVED ARTWORK. BATCH PRINTING AREA REMAINS UNVARNISHED			

May Breedlove
Digitally signed by May Breedlove
Date: 2019.07.18 15:40:13 -04'00'

Diana Marie Wood
18 July 2019

Carole Capella
Digitally signed by Carole Capella
Date: 2019.07.18 20:56:33 -04'00'

36 mm | 36 mm

Theophylline (Anhydrous) Extended-Release Tablets 52523

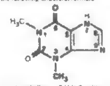
Theophylline (Anhydrous) Extended-Release Tablets 52523

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

DESCRIPTION

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

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



The molecular formula of anhydrous theophylline is $C_7H_8N_4O_2$ with a molecular weight of 180.17 g/mol.

Each extended-release tablet for oral administration contains 400 or 600 mg of anhydrous theophylline. Inactive ingredients: cetostearyl alcohol, hydroxyethyl cellulose, magnesium stearate, povidone and talc.

CLINICAL PHARMACOLOGY

Mechanism of Action

Theophylline has two distinct actions in the airways of patients with reversible obstruction; smooth muscle relaxation (i.e., bronchodilation) and suppression of the response of the airways to stimuli (i.e., non-bronchodilator prophylactic effects). While the mechanisms of action of theophylline are not known with certainty, studies in animals suggest that bronchodilatation is mediated by the inhibition of two isozymes of phosphodiesterase (PDE 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 (e.g., hypotension, tachycardia, headache, and emesis) and adenosine receptor antagonism (e.g., alterations in cerebral blood flow).

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

Serum Concentration-Effect Relationship

Bronchodilation occurs over the serum theophylline concentration range of 5 to 20 mcg/mL. Clinically [illegible]

Pharmacokinetics

[illegible] release solid oral dosage form. Theophylline does not undergo any appreciable pre-systemic elimination, distributes freely into fat-free tissues, and is extensively metabolized in the liver.

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

TABLE I. Mean and range of total body clearance and half-life of theophylline related to age and altered physiological states[¶]

Population Characteristics	Total body clearance* mean (range)[††] (mL/kg/min)	Half-life mean (range)[††] (hr)
Age		
Premature neonates		
postnatal age 3 to 15 days	0.29 (0.09 to 0.49)	30 (17 to 43)
postnatal age 25 to 57 days	0.64 (0.04 to 1.2)	20 (9.4 to 30.6)
Term infants		
postnatal age 1 to 2 days	NR[†]	25.7 (25 to 26.5)
postnatal age 3 to 30 weeks	NR[†]	11 (6 to 29)
Children		
1 to 4 years	1.7 (0.5 to 2.9)	3.4 (1.2 to 5.8)
4 to 12 years	1.6 (0.8 to 2.4)	NR[†]
13 to 15 years	0.9 (0.48 to 1.3)	NR[†]
6 to 17 years	1.4 (0.2 to 2.6)	3.7 (1.5 to 5.9)
Adults (16 to 60 years)		
otherwise healthy non-smoking asthmatics	0.65 (0.27 to 1.03)	8.7 (6.1 to 12.8)
Elderly (>60 years)		
non-smokers with normal cardiac, liver, and renal function	0.41 (0.21 to 0.61)	9.8 (1.6 to 18)
Concurrent illness or altered physiological state		
Acute pulmonary edema	0.33** (0.07 to 2.45)	19** (3.1 to 82)
COPD->60 years, stable non-smoker > 1 year	0.54 (0.44 to 0.64)	11 (9.4 to 12.6)
COPD with cor pulmonale	0.48 (0.08 to 0.88)	NR[†]
Cystic fibrosis (14 to 28 years)	1.25 (0.31 to 2.2)	6 (1.8 to 10.2)
Fever associated with acute viral respiratory illness (children 9 to 15 years)	NR[†]	7 (1 to 13)
Liver disease		
cirrhosis	0.31** (0.1 to 0.7)	32** (10 to 56)
acute hepatitis	0.35 (0.25 to 0.45)	19.2 (16.6 to 21.8)
cholestasis	0.65 (0.25 to 1.45)	14.4 (5.7 to 31.8)
Pregnancy		
1st trimester	NR[†]	8.5 (3.1 to 13.9)
2nd trimester	NR[†]	8.8 (3.8 to 13.8)
3rd trimester	NR[†]	13 (8.4 to 17.6)
Sepsis with multi-organ failure	0.47 (0.19 to 1.9)	18.8 (6.3 to 24.1)
Thyroid disease		
hypothyroid	0.38 (0.13 to 0.57)	11.6 (8.2 to 25)
hyperthyroid	0.8 (0.68 to 0.97)	4.5 (3.7 to 5.6)

[illegible]

NR = not reported or not reported in a comparable format.

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 administered in the fed state is completely absorbed after oral administration.

In a single-dose crossover study, two 400 mg theophylline extended-release tablets were administered to [illegible]

	MORNING	EVENING
AUC (0 to 24 hrs) (mcg hr/mL)	[illegible]	[illegible]
C_{max} (mcg/mL)	[illegible]	[illegible]
C_{min} (mcg/mL)	[illegible]	[illegible]
T_{max} (hours)	[illegible]	[illegible]

[illegible]

	Theophylline Extended-Release Tablets 600 mg	Reference Drug 400 mg
AUC (0 to 24 hours) (mcg hr/mL)	[illegible]	[illegible]
C_{max} (mcg/mL)	[illegible]	[illegible]
C_{min} (mcg/mL)	[illegible]	[illegible]
C_{max}-C_{min} diff	[illegible]	[illegible]

[illegible]

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

In another study the bioavailability of the 600 mg theophylline extended-release tablet was examined with [illegible]

[illegible]

	600 mg TABLET FED	600 mg (ONE + ONE-HALF 400 mg TABLETS) FED
AUC 0 to 24 hrs (mcg hr/mL)	208.77 ± 51.04	212.32 ± 56.29
C_{max} (mcg/mL)	12.91 ± 2.46	13.17 ± 3.11
C_{min} (mcg/mL)	5.52 ± 1.79	5.39 ± 1.95
T_{max} (hours)	8.67 ± 3.31	7.33 ± 3.35
Percent Fluctuation	188.73 ± 54.82	179.72 ± 28.49

[illegible]

PRECAUTIONS

[illegible]

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 (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.	Increases 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

(continued)

May Breedlove — Digitally signed by May Breedlove Date: 2019.07.18 15:46:56 -04'00'

Donna Marie Watt
18 JULY 2019

Carole Capella — Digitally signed by Carole Capella Date: 2019.07.18 21:00:03 -04'00'

GLENMARK PHARMACEUTICALS LTD.	DATE: 18.07.2019	PANTONE SHADE NO: Black	
PRODUCT NAME: LFT THEOPHYLLINE ER TAB 400-600MG US	PKG. DEV.:	[illegible]	
ITEM CODE: PE52523 VERSION: 0819-1	RA	Regulatory Text	
PHARMACODE: NA BARCODE: 52523	QA:	Entire Text	
COUNTRY: US	PRODUCTION:	Machine Suitability	
LOCATION: Goa	REMARKS NA		
PACK: Folded&glue 35x36mm			
ACTUAL SIZE: 490X280 MM			
SPECIFICATION: 40 GSM BIBLE PAPER			

Temple Packaging Pvt. Ltd. Sap code 40100010107 File 58284 Ver 03 shai

Lithium	Theophylline increases renal lithium clearance.	Lithium dose required to achieve a therapeutic serum concentration increased 21 ± 4 (range 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 disopyram.	80% increase
Midazolam	Similar to diazepam.	Similar to diazepam.
Mononycline	Increases theophylline clearance.	25% decrease
Pancuronium	Theophylline may antagonize non-depolarizing neuromuscular blocking effects, 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 two 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 to 40% decrease
St. John's Wort (Hypericum Perforatum)	Decrease in theophylline plasma concentrations.	Higher doses of theophylline may be required to achieve desired effect. Stopping St. John's Wort may result in theophylline toxicity.
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
Tolbutamide	Decreases theophylline clearance.	62% increase
Troleandomycin	Similar to erythromycin	33 to 100% increase depending on troleandomycin dose
Verapamil	Similar to diltiazem.	20% increase

* Refer to PRECAUTIONS, Drug Interactions for additional information regarding these drug interactions.
** Average effect on steady-state theophylline concentration or other clinical effect in pharmacological interaction. Individual patients may experience larger changes in serum theophylline concentration than the value listed.

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

albuterol, systemic and inhaled	metaproterenol
amoxicillin	methylprednisolone
ampicillin, with or without sulbactam	metronidazole
atenolol	nadolol
azithromycin	nizatidine
caffeine, dietary ingestion	nizoldipine
cefaclor	ofloxacin
cefuroxime	omeprazole
cephalexin	penicillin
clarithromycin	piroxicam
diltiazem	ranitidine
enoxacin	sorbitol
famotidine	sucralfate
felodipine	terbutaline
finasteride	tetracycline
flunisolide	ticlopidine
fluticasone	tocainide
hydrocortisone	triamcinolone
isoflurane	zafirlukast (prophylaxis dosing; do not exceed 40 mg/day)
isradipine	zileuton
ketoconazole	zolmitriptan
lansoprazole	zolpidem
metaproterenol	

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

Drug-Food Interactions

The bioavailability of theophylline (anhydrous) tablets has been studied with co-administration of food. In three single-dose studies, subjects given theophylline 400 mg or 600 mg tablets with a standardized high-fat meal were compared to fasted conditions. Under fed conditions, this meal altered rate of absorption and bioavailability was increased, however, a perceptible increase in the rate and extent of absorption was not evident (see **Pharmacokinetics, Absorption**). The increased rate and extent of absorption under fed conditions suggests that dosing should be ideally administered consistently either with or without food.

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, aminophylline, and pentoxifylline are not detected by these assays. Some drugs (e.g., cefazolin, cephalothin), however, may interfere with certain HPLC techniques. Caffeine and xanthine metabolites in neonates or patients with renal dysfunction may cause false readings from some dry reagent office methods to be higher than the actual serum theophylline concentration.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long term carcinogenicity studies have been carried out in mice (oral doses 30 to 100 mg/kg) and rats (oral doses 5 to 75 mg/kg). Results are pending.

Theophylline has been studied in Ames salmonella/ in vivo and in vitro cytogenetics, in vivo rat bone marrow cytogenetics, rat hepatocyte unscheduled DNA synthesis, and mouse lymphoma forward mutation assays. Theophylline was negative in all of these assays.

In a 14 week continuous breeding study, theophylline, administered to mating pairs of B6C3F1 mice at dose levels of 120, 270 and 609 mg/kg (approximately 1 to 3 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 12 week fertility studies, theophylline was administered to F344 rats and B6C3F1 mice at oral doses of 45 to 180 mg/kg (approximately 2 times the human dose on a mg/m² basis). At the high dose, systemic toxicity was observed in both species including decreases in fertility/pair weight.

Pregnancy: Teratogenic Effects: Category C

In studies in which pregnant mice, rats and rabbits were dosed during the period of organogenesis, theophylline produced teratogenic effects.

In studies with mice, a single intraperitoneal dose at and above 100 mg/kg (approximately equal to the maximum recommended oral dose for adults on a mg/m² basis) during organogenesis produced cleft palate and digital abnormalities. Micrognathia, micrognathia, clubfoot, subcutaneous hemorrhages, open eyelids, and polydactility were observed at doses that are approximately 7 times the maximum recommended oral dose for adults on a mg/m² basis.

In a study with rats dosed from conception through organogenesis, an oral dose of 160 mg/kg/day (approximately 2 times the maximum recommended oral dose for adults on a mg/m² basis) produced digital abnormalities. Embryolethality was observed with a subcutaneous dose of 200 mg/kg/day (approximately 4 times the maximum recommended oral dose for adults on a mg/m² basis).

In a study in which pregnant rabbits were dosed throughout organogenesis, an intravenous dose of 60 mg/kg/day (approximately 2 times the maximum recommended oral dose for adults on a mg/m² basis) which caused the death of two does and clinical signs of toxicity, produced cleft palate and were embryotoxic. Doses at and above 15 mg/kg/day (less than the maximum recommended oral dose for adults on a mg/m² basis) increased the incidence of skeletal variations.

There are no adequate and well-controlled studies in pregnant women. Theophylline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 also expected to parallel the serum concentration. An infant ingesting a little of breast milk containing 10 to 20 mg/dL of theophylline per day is likely to receive 10 to 20 mg of theophylline per day. Serious adverse effects in the infant are unlikely unless the mother has toxic serum theophylline concentrations.

Pediatric Use

Theophylline is safe and effective for the approved indications in pediatric patients. The pharmacokinetic dose of theophylline must be adjusted with caution in pediatric patients since the rate of theophylline clearance is highly variable across the pediatric age range (see **CLINICAL PHARMACOLOGY**, Table I, **DOSAGE AND ADMINISTRATION**, Table IV).

Geriatric Use

Elderly patients are at a significantly greater risk of experiencing serious toxicity from theophylline than younger patients due to pharmacokinetic and pharmacodynamic changes associated with aging. The clearance of theophylline is decreased by an average of 30% in healthy elderly subjects (>60 yrs) compared to healthy young adults. Theophylline clearance may be further reduced by concomitant diseases prevalent in the elderly, which further impair clearance of this drug and have the potential to increase serum levels and produce clinical toxicity. These conditions include congestive heart failure, chronic obstructive pulmonary disease, congestive heart failure, hepatic disease and an increased prevalence of use of certain medications (see **PRECAUTIONS**, Drug Interactions), with the potential for pharmacokinetic and pharmacodynamic interaction. Protein binding may be decreased in the elderly resulting in an increased proportion of the free 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. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in elderly patients (see **PRECAUTIONS, Monitoring Serum Theophylline Concentrations**, and **DOSAGE AND ADMINISTRATION**). 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 tolerate the drug well and the steady-state serum theophylline concentration is <10 mcg/mL (see **DOSAGE AND ADMINISTRATION**). Theophylline doses greater than 400 mg/d should be prescribed with caution in elderly patients.

ADVERSE REACTIONS

Adverse reactions associated with theophylline are generally mild when peak serum theophylline concentrations are <20 mcg/mL and rarely 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 of increasing severity including persistent vomiting, cardiac arrhythmias, and intractable seizures which can be lethal (see **OVERDOSAGE**). The transient caffeine-like adverse reactions occur in about 30% of patients when theophylline therapy is initiated at dosing rates that recommended initial doses (e.g., >300 mg/day in adults and >11 mg/kg/day in children beyond 1 year of age). During the initiation of theophylline therapy, caffeine-like adverse effects may be observed in patient tolerance, 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-specific 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 lower serum theophylline concentrations within the therapeutic range (i.e., 10 to 20 mcg/mL). Dosage reduction may alleviate the caffeine-like adverse effects in these patients. However, persistent adverse effects should result in a reevaluation of the need for continued theophylline therapy and the patient's therapeutic benefit of alternative treatment.

Other adverse reactions that have been reported at serum theophylline concentrations <20 mcg/mL include diarrhea, irritability, restlessness (may alternate with lethargy), and transient diuresis. 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 been similar to seizure activities associated with excessive serum theophylline concentrations resulting from an overdose (i.e., they have generally been transient, often stopped without anticonvulsant therapy, and do not result in neurological residua).

TABLE IV. Manifestations of theophylline toxicity.*

Sign/Symptom	Percentage of patients reported with sign or symptom			
	Acute Overdose (Large Single Ingestion)		Chronic Overdosage (Multiple Excessive Doses)	
	Study 1 (n = 157)	Study 2 (n = 14)	Study 1 (n = 88)	Study 2 (n = 102)
Convulsions	NR**	0	NR**	6
GI/Peritoneal				
Vomiting	73	93	30	61
Abdominal Pain	NR**	7	NR**	13
Diarrhea	NR**	0	NR**	12
Hematemesis	NR**	0	NR**	2
Metabolic/Other				
Hypokalemia	82	79	44	43
Hyperglycemia	69	NR**	18	NR**
Acid-base disturbance	34	21	3	3
Rhabdomyolysis	NR**		NR**	0
Cardiovascular				
Sinus tachycardia	100	89	100	62
Other supraventricular tachycardias	2	21	12	14
Ventricular premature beats	3	21	12	18
Atrial fibrillation or flutter	1	NR**	2	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**	27
Tremors	34	29	16	14
Disorientation	NR**	7	NR**	11
Seizures	7	14	14	5
Death	8	21	10	4

* These data are derived from two studies in patients with serum theophylline concentrations >30 mcg/mL. In the first study (Shannon RP—Boston), from 1985, 116 (149–63) patients were evaluated from 140 consecutive admissions of theophylline toxicity referred to a regional poison center for consultation. In the second study (Shannon RP—Boston), from 1986, 88 (62–76) adult case histories retrospectively collected from 156 cases with serum theophylline concentrations >30 mcg/mL among 8000 cases currently maintained for management of serum theophylline concentrations in three emergency departments. Differences in the incidence of manifestations of theophylline toxicity between the two studies may reflect sample selection as a result of study design (e.g., in Study #1, 48% of the patients had acute intoxications versus only 10% in Study #2) and referral mechanisms of study hospitals.

** 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 overdosage, e.g., ingestion of a single large excessive dose (>10 mg/kg), as occurs in the context of an attempted suicide or accidental medication error, and (2) chronic overdosage, i.e., ingestion of repeated doses that are excessive for the patient's rate of theophylline clearance. The latter presentation is common in chronic theophylline overdosage can complicate or aggravate error in dosing. Healthcare professionals prescribing of an extended dose or a normal dose in the presence of factors known to decrease the rate of theophylline clearance, and increasing the dose of theophylline as directed by measurements of symptoms without first measuring the serum theophylline can complicate or aggravate error in dosing. Healthcare professionals prescribing of an extended dose or a normal dose in the presence of factors known to decrease the rate of theophylline clearance, and increasing the dose of theophylline as directed by measurements of symptoms without first measuring the serum theophylline can contribute to determine whether a dose increase is safe.

Severe toxicity from theophylline overdose as a relatively rare event. Acute fatal/near fatal overdosage poisonings. The frequency of hospital admissions for acute overdosage of theophylline was about 1 per 1000 person-years exposure. In another study, among 6000 blood samples obtained for measurement of serum theophylline concentrations for any reason, from patients treated at an emergency department. This was a rate of 32 to 64 mg/mL range and 2% were >30 mcg/mL. Approximately two-thirds of the patients with serum theophylline concentrations in the 30 to 60 mcg/mL range had one or more manifestations of toxicity while >80% of patients with serum theophylline concentrations >30 mcg/mL were clinically intoxicated. Similarly, in other reports, serious toxicity in children 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 dysrhythmias, 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, e.g., patients with neurological disorders have an increased risk of seizures; patients with congestive heart failure have 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 overdosage (acute and chronic overdose) are listed in Table IV.

Other manifestations of theophylline toxicity include increases in the CBC, hyperglycemia, myoglobinuria and leukocytic 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 pharmacological 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 carrying 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 initial presentation of the patient for medical care.)

1. While simultaneously maintaining important vitals, a regional poison center / clinical toxicologist 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 mortality and morbidity associated with theophylline-induced seizures, treatment should be rapid and aggressive. Anticonvulsant therapy should be initiated with an intravenous benzodiazepine, e.g., diazepam in increments of 0.1 to 0.2 mg/kg every 1 to 2 minutes until seizures are terminated. Repetitive seizures should be treated with a loading dose of phenobarbital (20 mg/kg infused over 30 to 60 minutes). Case reports of theophylline overdose in humans and animal studies suggest that phenytoin is ineffective in terminating theophylline-induced seizures. The benzodiazepines and phenobarbital required to terminate theophylline-induced seizures are of sufficient doses that may cause severe respiratory depression or respiratory arrest. The healthcare professional should therefore be prepared to provide assisted ventilation. Elderly patients and patients with COPD are at increased risk of developing respiratory depression at lower doses of benzodiazepines. Barbiturates, alone 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 catecholamine-induced arrhythmias by theophylline. Enflurane appears less likely to be associated with this direct 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. Antiemetic Used for Anticholinergics In patients with theophylline overdose who are at high risk for theophylline-induced seizures (i.e., 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 intravenous 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 enhanced removal of theophylline (e.g., transfer of a high risk patient from one healthcare facility to another for extracorporeal treatment) and clinical circumstances (e.g., overnight intubation with plans to extubate the patient the next morning) where short acting drugs may not be technically feasible or a patient with vomiting unresponsive to antiemetics who is unable to tolerate multiple oral activated charcoal). In general, prophylactic anticonvulsant therapy is not indicated in patients with acute overdoses who are likely to delay the onset of theophylline-induced generalized seizures and to increase the dose of theophylline required to induce seizures (i.e., markedly increases the V_d). Although there are no controlled studies in humans, a loading dose of intravenous phenobarbital (20 mg/kg infused over 60 minutes) may safely and effectively be used in most patients who are at high risk for seizures while other methods 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 correlate poorly with reduced 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 (5.5 g/kg up to 20 g and repeat at least once 1 to 2 hours after the first dose) is extremely effective in blocking the absorption of theophylline throughout the gastrointestinal tract, even when administered several hours after ingestion. If the patient is vomiting, the charcoal should be administered through a nasogastric tube or after antiemetic administration. Antiemetics administered such as prochlorperazine or perphenazine should be avoided since they can lower the seizure threshold and frequently cause dyskinetic reactions. A single dose of sorbitol may be used to promote cathartic 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 preparations 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. Isolated abnormalities of fluid and electrolyte abnormalities should be promptly corrected. Monitoring and treatment should be continued until the serum concentration decreases below 20 mcg/mL.
7. Enhance clearance of theophylline: Multiple-dose oral activated charcoal (e.g. 0.5 mg/kg up to 20 g every two hours) increases the clearance of theophylline at least twofold by adsorption of theophylline excreted into gastrointestinal fluids. Charcoal must be released in, and pass through, the gastrointestinal tract to be effective; serious toxicity 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 given concomitant with the activated charcoal to promote smoking to facilitate clearance of the absorbed theophylline from the gastrointestinal tract. Sorbitol alone does not enhance clearance of theophylline and should be dosed with caution to prevent excessive diarrhea, which can result in severe fluid and electrolyte imbalances. Commercially available liquid 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 >30 ≤60 mcg/mL

1. Administration of a single dose of oral activated charcoal.
2. Monitor the patient and obtain a serum theophylline concentration every 2 to 4 hours to gauge the effectiveness of therapy and to guide further treatment decisions.

B. Serum Concentration >60 ≤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 or patients ≥16 years of age

1. Consider prophylactic anticonvulsants.
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

Comparing 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 as much as fivefold, but serious complications, including thrombosis, hypocalcemia, platelet consumption and bleeding diathesis may occur. Hemodialysis is about as efficient as multiple-dose oral activated charcoal and has a lower risk of serious complications. High 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

Theophylline 400 or 600 mg extended-release tablets can be taken once a day, in the morning or evening. It is recommended that theophylline extended-release tablets be taken with meals. Patients should be advised that if they choose to take theophylline extended-release tablets with food, it should be taken consistently with food and if they take it on a fasted condition it should routinely be taken fasted. It is important that the product selected should be dosed consistently with or without food.

Theophylline extended-release tablets are not to be chewed or crushed because it may lead to a rapid release of theophylline with the potential for toxicity. The tablet may be split. Infrequently, patients receiving theophylline extended-release tablets 400 mg or 600 mg tablets may pass an intact matrix tablet in the stool or via colostomy. These matrix tablets usually contain little or no residual theophylline.

Adolescent patients, 12 years of age or older who are taking an immediate-release or controlled-release theophylline product may be transferred to once-daily administration of 400 mg or 600 mg theophylline extended-release tablets on a mg-for-mg basis.

It must be recognized that the peak and trough serum theophylline levels produced by this once-daily dosing may vary from those produced by the previous product and/or regimen.

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 intrinsic 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 by about a factor of nine in otherwise healthy individuals of factors known to alter theophylline clearance (e.g., 400 to 1600 mg/day in adults >60 years old and 100 to 900 mg/day in children 1 to 9 years old). For a given population there is no single theophylline dose that will provide both safe and effective serum concentrations for all patients. Administration of the initial theophylline dose required to achieve a therapeutic serum theophylline concentration in a given population may result in either sub-therapeutic or potentially toxic serum theophylline concentrations in individual patients. For example, at a dose of 900 mg/d in adults <60 years or 22 mg/kg/d 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 minimized in most patients by starting with a sufficiently low dose and slowly increasing the dose if judged to be clinically indicated in small increments (See Table V). Dose increases should only be made if the previous dosage is well tolerated and at intervals of no less than 3 days to allow serum theophylline concentrations to reach the new steady-state. Dosage adjustment should be guided by serum theophylline concentration measurement (see **PRECAUTIONS, Laboratory Tests** and **DOSAGE AND ADMINISTRATION**, Table VI). 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, e.g., every 24 hours.

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

Table IV contains theophylline dosing titration schemes recommended for patients of various age groups and clinical circumstances. Table VI contains recommendations for theophylline dosage adjustment based upon serum theophylline concentrations.

Adults With Risk Factors For Impaired Clearance, The Elderly (>60 Years), And Those In Whom It Is Not Feasible to Monitor Serum Theophylline Concentrations

In otherwise healthy adult patients who are elderly, the recommended dose is 16 mg/kg/day 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 otherwise healthy adult patients who are elderly, the recommended dose is 12 mg/kg/day 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.

[illegible] dosage should be reduced by approximately 50% in patients with cor pulmonale who have developed congestive heart failure, hepatic disease, or fever, and in patients taking drugs that interfere with theophylline's clearance (see **PRECAUTIONS, Drug Interactions**). The first dose should not exceed 250 mg/day in these patients. Subsequent dosage should be adjusted on the basis of serum theophylline concentration measurements.

TABLE V. Dosage initiation and titration (as anhydrous theophylline) *

A. Children 232 to 16 years of age (50 to 80 years) without risk factors for impaired clearance.

Titration Step	Children > 45 kg	Children > 45 kg and adults
1. Starting Dosage	12 to 14 mg/kg/day q24h maximum of 300 mg/day (dose: 00*)	300 to 400 mg/day (dose: 00*)
2. After 3 days, if tolerated increase dose to	16 mg/kg/day up to a maximum of 400 mg/day (dose: 00*)	400 to 600 mg/day (dose: 00*)
3. After 3 more days, if tolerated, and if needed increase dose to	20 mg/kg/day up to a maximum of 600 mg/day (dose: 00*)	As with all theophylline products, fitness greater than 600 mg should be titrated according to blood level rate, after 3 days.

If theophylline dosage should be titrated to a dose that is not a multiple of the tablet strength, the next lower dose should be used.

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 otherwise [illegible] adult patients who are elderly, the recommended dose is 16 mg/kg/day 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 otherwise healthy adult patients who are elderly, the recommended dose is 12 mg/kg/day 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.

[illegible] dosage should be reduced by approximately 50% in patients with cor pulmonale who have developed congestive heart failure, hepatic disease, or fever, and in patients taking drugs that interfere with theophylline's clearance (see **PRECAUTIONS, Drug Interactions**). The first dose should not exceed 250 mg/day in these patients. Subsequent dosage should be adjusted on the basis of serum theophylline concentration measurements.

TABLE VI. Dosage adjustment guided by serum theophylline concentrations.

Peak Serum Theophylline Concentration	Dosage Adjustment
<5.5 mcg/mL	If symptoms are not controlled and current dosage is tolerated, increase dose about 25%. Recheck serum concentration after three days for further dosage adjustment.
5.5 to 10.5 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.
10.5 to 19.5 mcg/mL	Consider 10% decrease in dose to provide greater margin of safety even if current dosage is tolerated.‡
20 to 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 to 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 overdose).
> 30 mcg/mL	Treat overdosage 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.

† Each individual and/or small therapeutic serum [illegible] is acceptable. Serum theophylline [illegible] are greater than 20 mcg/mL, [illegible] that can occur [illegible] if a therapeutic serum [illegible] is [illegible] theophylline is added or discontinued (see **DRUG INTERACTIONS**).

‡ Consider [illegible] if the patient is [illegible] theophylline [illegible] serum [illegible] is [illegible] theophylline [illegible] is [illegible] or discontinued (see **DRUG INTERACTIONS**).

HOW SUPPLIED

Theophylline (Anhydrous) Extended-Release Tablets, 400 mg are supplied in:
100 count UNIT-DOSE bottles NDC 68462-386-01
500 count non-CPC bottles NDC 68462-386-05

Each white to off-white, round shaped, uncoated 400 mg tablet is debossed with 'GM' on either side of the tablet line and '400' on the other side.

Theophylline (Anhydrous) Extended-Release Tablets, 600 mg are supplied in:
100 count CPC bottles NDC 68462-388-01
500 count non-CPC bottles NDC 68462-388-05

Each white to off-white, oval shaped, uncoated 600 mg tablet is debossed with 'GM' on either side of the tablet line and '600' on the other side.

STORAGE

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Dispense in a tight, light-resistant container.

Manufactured by
Glenmark Pharmaceuticals Limited
Colvale-Bardez, Goa 403 513, India

Manufactured for

Glenmark Pharmaceuticals Inc., USA
Mahwah, NJ 07430
Consumer Tel: 1 (888) 721-7115
www.glenmarkpharma-us.com

July 2019

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May Breedlove

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Donnamarie Watt
18 JULY 2019

GLENMARK PHARMACEUTICALS LTD.		DATE: 18.07.2019	PANTONE SHADE NO: Black
PRODUCT NAME: LPT THEOPHYLLINE ER TAB 400-600MG U		PKG. DEV.:	Spec sheet, Version Consistency of Design, packaging shop, Pack size, Dimensions & Leaflet
ITEM CODE: PES2523	VERSION: 0619-1		
PHARMACODE: NA	BARCODE: SEMO	RA	Regulatory Text
COUNTRY: US		QA:	Bar Code Text
LOCATION: Goa		PRODUCTION:	Machine Suitability
PACK: Folded&glue 35x26mm		REMARKS: NA	
ACTUAL SIZE: 480X280 MM			
SPECIFICATION: 40 GSM BIBLE PAPER			

Temple Packaging Pvt. Ltd. Sap code: 40100010107 File: 58284 Ver. 03 / sharp

Carole Capella

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Date: 2019.07.18 20:59:34 -04'00'

MARKET WITHDRAWAL RETURN RESPONSE FORM
THEOPHYLLINE EXTENDED-RELEASE TABLETS USP 400mg
100s Container pack (Tablets)
(NDC 68462-380-01)
Retail Level
8/8/2025

Please fill out this form completely. By doing so, this will acknowledge that you have read and understand the withdrawal instructions and have taken the appropriate action.

Customer Name:	DEA#:

DEA # is required, if it is not provided, the processing of your form will be delayed.

Address:		
City:	State:	Zip:
Contact Name (Please Print):		
Telephone#:	Email:	
Contact Signature:	Date:	
DEBIT MEMO# (If unsure, leave blank):		

Wholesaler Information if not directly purchased from Glenmark Pharmaceuticals Inc.:

Wholesaler Name:	DEA#:	
City:	State:	Zip:

I have checked my stock and communicated to my customers at the appropriate level:

□ I confirm that all locations that received the impacted products have been notified to the Retail level _____(Initial and date)

□ I do not have any stock of the market withdrawn items. **OR**

□ I have quarantined and listed in the box below the quantity of market withdrawn units and I will be returning to Inmar, as soon as possible. Upon receipt of this Response Form, Inmar, will issue return authorization label(s) Please indicate the # of needed box labels_____

Theophylline Extended-Release Tablets USP 400mg (100's Tablets)

Sr. No.	NDC Code	Batch No.	Pack Size	Exp. Date	Total Full/ Sealed and Partial/ Open Bottle Count
1	68462-380-01	19233993	100's Tablets	Sep-2025	
2	68462-380-01	19234027	100's Tablets	Sep-2025	
3	68462-380-01	19234047	100's Tablets	Sep-2025	
4	68462-380-01	19234070	100's Tablets	Sep-2025	
5	68462-380-01	19234079	100's Tablets	Sep-2025	
6	68462-380-01	19234093	100's Tablets	Sep-2025	
7	68462-380-01	19234114	100's Tablets	Sep-2025	
8	68462-380-01	19234385	100's Tablets	Oct-2025	
9	68462-380-01	19234427	100's Tablets	Oct-2025	
10	68462-380-01	19234459	100's Tablets	Oct-2025	
11	68462-380-01	19234462	100's Tablets	Oct-2025	
12	68462-380-01	19240385	100's Tablets	Dec-2025	
13	68462-380-01	19240437	100's Tablets	Jan-2026	
14	68462-380-01	19241185	100's Tablets	Feb-2026	
15	68462-380-01	19241197	100's Tablets	Feb-2026	
16	68462-380-01	19241220	100's Tablets	Feb-2026	
17	68462-380-01	19241238	100's Tablets	Feb-2026	
18	68462-380-01	19244538	100's Tablets	Oct-2026	
19	68462-380-01	19250174	100's Tablets	Dec-2026	

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