

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 74-962

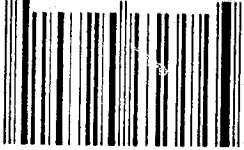
PRINTED LABELING

Manufactured by
**UPSHER-SMITH
LABORATORIES, INC.**
Minneapolis, MN 55447
Rev. 0497
49-02701



PENTOXIL 400 mg

NDC 0245-0027-01



NDC 0245-0027-01
Unit Dose, 100 Tablets

PENTOXIL™

**Pentoxifylline
Extended-release Tablets**

400 mg

TAKE WITH MEALS.

UPSHER-SMITH

Each tablet contains: Pentoxifylline 400 mg
Usual dosage: See insert for full prescribing information.
Store at controlled room temperature 15-30°C (59-86°F).
Protect tablets from light.
**STORE THIS AND ALL MEDICATION OUT OF THE REACH
OF CHILDREN.**

SAMPLE

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MAR 31 1999

APPROVED

NDC 0245-0027-01
Unit Dose, 100 Tablets

PENTOXIL™

CAUTION: Federal law prohibits dispensing without prescription.

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

**Pentoxifylline
Extended-release Tablets**

400 mg

TAKE WITH MEALS.

UPSHER-SMITH

Margo

Pentoxil Bottle of 100 Label

Each tablet contains:
Pentoxitylline 400 mg

Usual dosage: See insert for full
prescribing information.

Dispense in well-closed, light-
resistant containers with safety
closures.

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

**STORE THIS AND ALL MEDICATION
OUT OF THE REACH OF CHILDREN.**

NDC 0245-0027-11
100 Tablets

PENTOXIL™

Pentoxitylline
Extended-release Tablets

400 mg

TAKE WITH MEALS.

UPSHER-SMITH

CAUTION: Federal law prohibits
dispensing without prescription.

Do not use if bottle closure
seal is broken.

Manufactured by
UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447
Rev. 0497 42-02711



N
3 0245-0027-11 9

SAMPLE
Lot/Exp.

Manjo

Pentoxil Unit Dose Card - Blister Text

NOTE: Text with lot number and expiration date are imprinted on-line during the unit-dose packaging process.

TAKE WITH MEALS.
PENTOXIL™
Pentoxifyline
Extended-release
Tablet, 400 mg
UPsher-SMITH
MINNEAPOLIS, MN 55447
Rev. 0796

LOT NO.
EXP.

TAKE WITH MEALS.
PENTOXIL™
Pentoxifyline
Extended-release
Tablet, 400 mg
UPsher-SMITH
MINNEAPOLIS, MN 55447
Rev. 0796

LOT NO.
EXP.

TAKE WITH MEALS.
PENTOXIL™
Pentoxifyline
Extended-release
Tablet, 400 mg
UPsher-SMITH
MINNEAPOLIS, MN 55447
Rev. 0796

LOT NO.
EXP.

TAKE WITH MEALS.
PENTOXIL™
Pentoxifyline
Extended-release
Tablet, 400 mg
UPsher-SMITH
MINNEAPOLIS, MN 55447
Rev. 0796

LOT NO.
EXP.

TAKE WITH MEALS.
PENTOXIL™
Pentoxifyline
Extended-release
Tablet, 400 mg
UPsher-SMITH
MINNEAPOLIS, MN 55447
Rev. 0796

LOT NO.
EXP.

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PENTOXIL™
Pentoxifyline
Extended-release
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Rev. 0796

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EXP.

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Rev. 0796

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Tablet, 400 mg
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Pentoxifyline
Extended-release
Tablet, 400 mg
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Rev. 0796

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PENTOXIL™
Pentoxifyline
Extended-release
Tablet, 400 mg
UPsher-SMITH
MINNEAPOLIS, MN 55447
Rev. 0796

LOT NO.
EXP.

TAKE WITH MEALS.
PENTOXIL™
Pentoxifyline
Extended-release
Tablet, 400 mg
UPsher-SMITH
MINNEAPOLIS, MN 55447
Rev. 0796

LOT NO.
EXP.

001 10 011

Pentoxil Bottle of 5000 Label

U.S. 30

NDC 0245-0027-55
5000 Tablets

PENTOXILTM

**Pentoxifylline
Extended-release
Tablets**

400 mg

TAKE WITH MEALS.

UPSHER-SMITH

Each tablet contains:

Pentoxifylline 400 mg

Usual dosage: See insert for full prescribing information.

This is a bulk package intended for further repackaging.

Dispense in well-closed, light-resistant containers with safety closures.

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

STORE THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

CAUTION: Federal law prohibits dispensing without prescription.

Do not use if bottle closure seal is broken.



SAMPLE

Manufactured by
UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447
Rev. 0497

42-02755

Lot/Exp

Pentoxil Bottle of 500 Label

Mag

NDC 0245-0027-15
500 Tablets

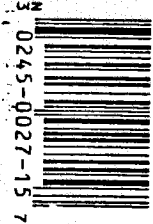
PENTOXIL™

**Pentoxifylline
Extended-release Tablets**

400 mg

TAKE WITH MEALS.

UPSHER-SMITH



Each tablet contains:
Pentoxifylline 400 mg

Usual dosage: See insert for full prescribing information.

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

STORE THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

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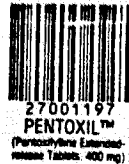
Manufactured by
UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447
Rev. 0497

42-02715

Lot/Exp.

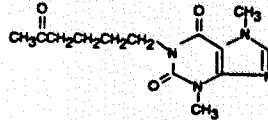
SAMPLE

PENTOXIL™
(Pentoxifylline
Extended-release
Tablets, 400 mg)



DESCRIPTION:

Pentoxil™ (Pentoxifylline Extended-release Tablets) for oral administration contain 400 mg of the active drug and the following inactive ingredients: D&C Red No. 27 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, hydroxypropyl methylcellulose USP, magnesium stearate NF, polyethylene glycol NF, polysorbate 80 NF, povidone USP, silicon dioxide NF and titanium dioxide USP, in an extended-release formulation. Pentoxil™ is a tri-substituted xanthine derivative designated chemically as 3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1H-purine-2,6-dione that, unlike theophylline, is a hemorrheologic agent, i.e., an agent that affects blood viscosity. Pentoxifylline is soluble in water and ethanol, and sparingly soluble in toluene. The structural formula is:



Molecular formula: C₁₃H₁₈N₄O₃ Molecular weight: 278.31

CLINICAL PHARMACOLOGY:

Mode of Action: Pentoxifylline and its metabolites improve the flow properties of blood by decreasing its viscosity. In patients with chronic peripheral arterial disease, this increases blood flow to the affected microcirculation and enhances tissue oxygenation. The precise mode of action of pentoxifylline and the sequence of events leading to clinical improvement are still to be defined. Pentoxifylline administration has been shown to produce dose related hemorrheologic effects, lowering blood viscosity, and improving erythrocyte flexibility. Leukocyte properties of hemorrheologic importance have been modified in animal and *in vitro* human studies. Pentoxifylline has been shown to increase leukocyte deformability and to inhibit neutrophil adhesion and activation. Tissue oxygen levels have been shown to be significantly increased by therapeutic doses of pentoxifylline in patients with peripheral arterial disease.

Pharmacokinetics and Metabolism: After oral administration in aqueous solution pentoxifylline is almost completely absorbed. It undergoes a first-pass effect and the various metabolites appear in plasma very soon after dosing. Peak plasma levels of the parent compound and its metabolites are reached within 1 hour. The major metabolites are Metabolite I (1-[5-hydroxyhexyl]-3,7-dimethylxanthine) and Metabolite V (1-[3-carboxypropyl]-3,7-dimethylxanthine), and plasma levels of these metabolites are 5 and 8 times greater, respectively, than pentoxifylline.

Following oral administration of aqueous solutions containing 100 to 400 mg of pentoxifylline, the pharmacokinetics of the parent compound and Metabolite I are dose-related and not proportional (non-linear), with half-life and area under the blood-level time curve (AUC) increasing with dose. The elimination kinetics of Metabolite V are not dose-dependent. The apparent plasma half-life of pentoxifylline varies from 0.4 to 0.8 hours and the apparent plasma half-lives of its metabolites vary from 1 to 1.6 hours. There is no evidence of accumulation or enzyme induction (Cytochrome P450) following multiple oral doses.

Excretion is almost totally urinary; the main biotransformation product is Metabolite V. Essentially no parent drug is found in the urine. Despite large variations in plasma levels of parent compound and its metabolites, the urinary recovery of Metabolite V is consistent and shows dose proportionality. Less than 4% of the administered dose is recovered in feces. Food intake shortly before dosing delays absorption of an immediate-release dosage form but does not affect total absorption. The pharmacokinetics and metabolism of pentoxifylline has not been studied in patients with renal and/or hepatic dysfunction, but AUC was increased and elimination rate decreased in an older population (60-68 years) compared to younger individuals (22-30 years).

After administration of the 400 mg controlled release pentoxifylline tablet, plasma levels of the parent compound and its metabolites reach their maximum within 2 to 4 hours and remain constant over a controlled period of time. Coadministration of pentoxifylline extended-release tablets with meals resulted in an increase in mean C_{max} and AUC by about 28% and 13% for pentoxifylline, respectively. C_{max} for metabolite M₁ also increased by about 20%. The controlled release of pentoxifylline from the tablet eliminates peaks and troughs in plasma levels for improved gastrointestinal tolerance.

INDICATIONS AND USAGE:

Pentoxil™ (Pentoxifylline Extended-release Tablets) is indicated for the treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs. Pentoxil™ can improve function and symptoms but is not intended to replace more definitive therapy, such as surgical bypass, or removal of arterial obstructions when treating peripheral vascular disease.

CONTRAINDICATIONS:

Pentoxil™ (Pentoxifylline Extended-release Tablets) should not be used in patients with recent cerebral and/or retinal hemorrhage or in patients who have previously exhibited intolerance to this product or methylxanthines such as caffeine, theophylline, and theobromine.

PRECAUTIONS:

General: Patients with chronic occlusive arterial disease of the limbs frequently show other manifestations of arteriosclerotic disease. Pentoxifylline has been used safely for treatment of peripheral arterial disease in patients with concurrent coronary artery and cerebrovascular diseases, but there have been occasional reports of angina, hypotension, and arrhythmia. Controlled trials do not show that pentoxifylline causes such adverse effects more often than placebo, but, as it is a methylxanthine derivative, it is possible some individuals will experience such responses. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration, cerebral and/or retinal bleeding) should have periodic examinations for bleeding including hematocrit and/or hemoglobin.

Drug Interactions: Although a causal relationship has not been established, there have been reports of bleeding and/or prolonged prothrombin time in patients treated with pentoxifylline with and without anticoagulants or platelet aggregation inhibitors. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration), should have periodic examinations for bleeding including hematocrit and/or hemoglobin. Concomitant administration of pentoxifylline and theophylline-containing drugs leads to increased theophylline levels and theophylline toxicity in some individuals. Such patients should be closely monitored for signs of toxicity and have their theophylline dosage adjusted as necessary. Pentoxifylline has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, antidiabetic agents, and antiarrhythmics, without observed problems. Small decreases in blood pressure have been observed in some patients treated with pentoxifylline; periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensive therapy. If indicated, dosage of the antihypertensive agents should be reduced.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies of the carcinogenic potential of pentoxifylline were conducted in mice and rats by dietary administration of the drug at doses up to 450 mg/kg (approximately 19 times the maximum recommended human daily dose (MRHD) in both species when based on body weight; 1.5 times the MRHD in the mouse and 3.3 times the MRHD in the rat when based on body surface area). In mice, the drug was administered for 18 months, whereas in rats, the drug was administered for 18 months followed by an additional 6 months without drug exposure. In the rat study, there was a statistically significant increase in benign mammary fibroadenomas in females of the 450 mg/kg group. The relevance of this finding to

recovery of Metabolite V is consistent and shows dose proportionality. Less than 4% of the administered dose is recovered in feces. Food intake shortly before dosing delays absorption of an immediate-release dosage form but does not affect total absorption. The pharmacokinetics and metabolism of pentoxifylline has not been studied in patients with renal and/or hepatic dysfunction, but AUC was increased and elimination rate decreased in an older population (60-68 years) compared to younger individuals (22-30 years).

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CONTRAINDICATIONS:

Pentoxil[®] (Pentoxifylline Extended-release Tablets) should not be used in patients with recent cerebral and/or retinal hemorrhage or in patients who have previously exhibited intolerance to this product or methylxanthines such as caffeine, theophylline, and theobromine.

PRECAUTIONS:

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Pregnancy: Teratogenic Effects: Pregnancy Category C. Teratogenicity studies have been performed in rats and rabbits, using oral doses up to 576 and 264 mg/kg, respectively. On a weight basis, these doses are 24 and 11 times the maximum recommended human dose (MRHD); on a body-surface-area basis, they are 4.2 and 3.5 times the MRHD. No evidence of fetal malformation was observed. Increased resorption was seen in rats of the 576 mg/kg group. There are no adequate and well controlled studies in pregnant women. Pentoxil[®] (Pentoxifylline Extended-release Tablets) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Pentoxifylline and its metabolites are excreted in human milk. Because of the potential for tumorigenicity shown for pentoxifylline in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

PENTOXIL™
(Pentoxifylline
Extended-release
Tablets, 400 mg)



ADVERSE REACTIONS:

Clinical trials were conducted using either extended-release pentoxifylline tablets for up to 60 weeks or immediate-release pentoxifylline capsules for up to 24 weeks. Dosage ranges in the tablet studies were 400 mg bid to bid and in the capsule studies, 200-400 mg bid. The table summarizes the incidence (in percent) of adverse reactions considered drug related, as well as the numbers of patients who received extended-release pentoxifylline tablets, immediate-release pentoxifylline capsules, or the corresponding placebos. The incidence of adverse reactions was higher in the capsule studies (where dose related increases were seen in digestive and nervous system side effects) than in the tablet studies. Studies with the capsule include domestic experience, whereas studies with the extended-release tablets were conducted outside the U.S. The table indicates that in the tablet studies few patients discontinued because of adverse effects.

INCIDENCE (% OF SIDE EFFECTS)

	Extended-Release Tablets		Immediate-Release Capsules	
	Commercially Available		Used Only for Controlled Clinical Trials	
	PENTOXIFYLLINE	PLACEBO	PENTOXIFYLLINE	PLACEBO
(Number of Patients at Risk)	(321)	(128)	(177)	(138)
Discontinued for Side Effect	3.1	0	9.6	7.2
CARDIOVASCULAR SYSTEM				
Angina/Chest Pain	0.3	-	1.1	2.2
Arrhythmia/Palpitation	-	-	1.7	0.7
Flushing	-	-	2.3	0.7
DIGESTIVE SYSTEM				
Abdominal Discomfort	-	-	4.0	1.4
Belching/Flatus/Bloating	0.6	-	9.0	3.6
Diarrhea	-	-	3.4	2.9
Dyspepsia	2.8	4.7	9.6	2.9
Nausea	2.2	0.8	28.8	8.7
Vomiting	1.2	-	4.5	0.7
NERVOUS SYSTEM				
Agitation/Nervousness	-	-	1.7	0.7
Dizziness	1.9	3.1	11.9	4.3
Drowsiness	-	-	1.1	5.8
Headache	1.2	1.6	6.2	5.8
Insomnia	-	-	2.3	2.2
Tremor	0.3	0.8	-	-
Blurred Vision	-	-	2.3	1.4

Pentoxifylline tablets have been marketed in Europe and elsewhere since 1972. In addition to the above symptoms, the following have been reported spontaneously since marketing or occurred in other clinical trials with an incidence of less than 1%; the causal relationship was uncertain.

- Cardiovascular - dyspnea, edema, hypotension.
- Digestive - anorexia; cholecystitis, constipation, dry mouth/thirst.
- Nervous - anxiety, confusion, depression, seizures.
- Respiratory - epistaxis, flu-like symptoms, laryngitis, nasal congestion.
- Skin and Appendages - brittle fingernails, pruritus, rash, urticaria, angioedema.
- Special Senses - blurred vision, conjunctivitis, earache, scotoma.
- Miscellaneous - bad taste, excessive salivation, leukopenia, malaise, sore throat/swollen neck glands, weight change.

A few rare events have been reported spontaneously worldwide since marketing in 1972. Although they occurred under circumstances in which a causal relationship with pentoxifylline could not be established, they are listed to serve as information for physicians: Cardiovascular—angina, arrhythmia, tachycardia, anaphylactoid reactions. Digestive—hepatitis, jaundice, increased liver enzymes; and Hemic and Lymphatic—decreased serum fibrinogen, pancytopenia, aplastic anemia, leukemia, purpura, thrombocytopenia.

OVERDOSAGE:

Overdosage with pentoxifylline has been reported in children and adults. Symptoms appear to be dose related. A report from a poison control center on 44 patients taking overdoses of enteric-coated pentoxifylline tablets noted that symptoms usually occurred 4-5 hours after ingestion and lasted about 12 hours. The highest amount ingested was 80 mg/kg; flushing, hypotension, convulsions, somnolence, loss of consciousness, fever, and agitation occurred. All patients recovered.

In addition to symptomatic treatment and gastric lavage, special attention must be given to supporting respiration, maintaining systemic blood pressure, and controlling convulsions. Activated charcoal has been used to absorb pentoxifylline in patients who have overdosed.

DOSAGE AND ADMINISTRATION:

The usual dosage of Pentoxil™ (Pentoxifylline Extended-release Tablets) in extended-release tablet form is one tablet (400 mg) three times a day with meals.

While the effect of Pentoxil™ (Pentoxifylline Extended-release Tablets) may be seen within 2 to 4 weeks, it is recommended that treatment be continued for at least 6 weeks. Efficacy has been demonstrated in double-blind clinical studies of 6 months duration.

Digestive and central nervous system side effects are dose related. If patients develop these effects it is recommended that the dosage be lowered to one tablet twice a day (800 mg/day). If side effects persist at this lower dosage, the

Insomnia			2.3	2.2
Tremor	0.3	0.8	-	-
Blurred Vision	-	-	2.3	1.4

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- Nervous - anxiety, confusion, depression, seizures.
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Digestive and central nervous system side effects are dose related. If patients develop these effects it is recommended that the dosage be lowered to one tablet twice a day (800 mg/day). If side effects persist at this lower dosage, the administration of Pentoxil[®] (Pentoxifylline Extended-release Tablets) should be discontinued.

HOW SUPPLIED:

Pentoxil[®] (Pentoxifylline Extended-release Tablets) is available for oral administration as 400 mg light-pink, unscored, film-coated, capsule-shaped tablets imprinted U-S 027; supplied in bottles of 100 (NDC 0245-0027-11); bottles of 500 (NDC 0245-0027-15); bottles of 5000 (NDC 0245-0027-55), and Unit Dose Packs of 100 (NDC 0245-0027-01).

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

Dispense in well-closed, light-resistant containers.

Protect blisters from light.

Manufactured by
 UPSHER-SMITH LABORATORIES, INC.
 Minneapolis, MN 55447

UPSHER-SMITH

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