

diabetes

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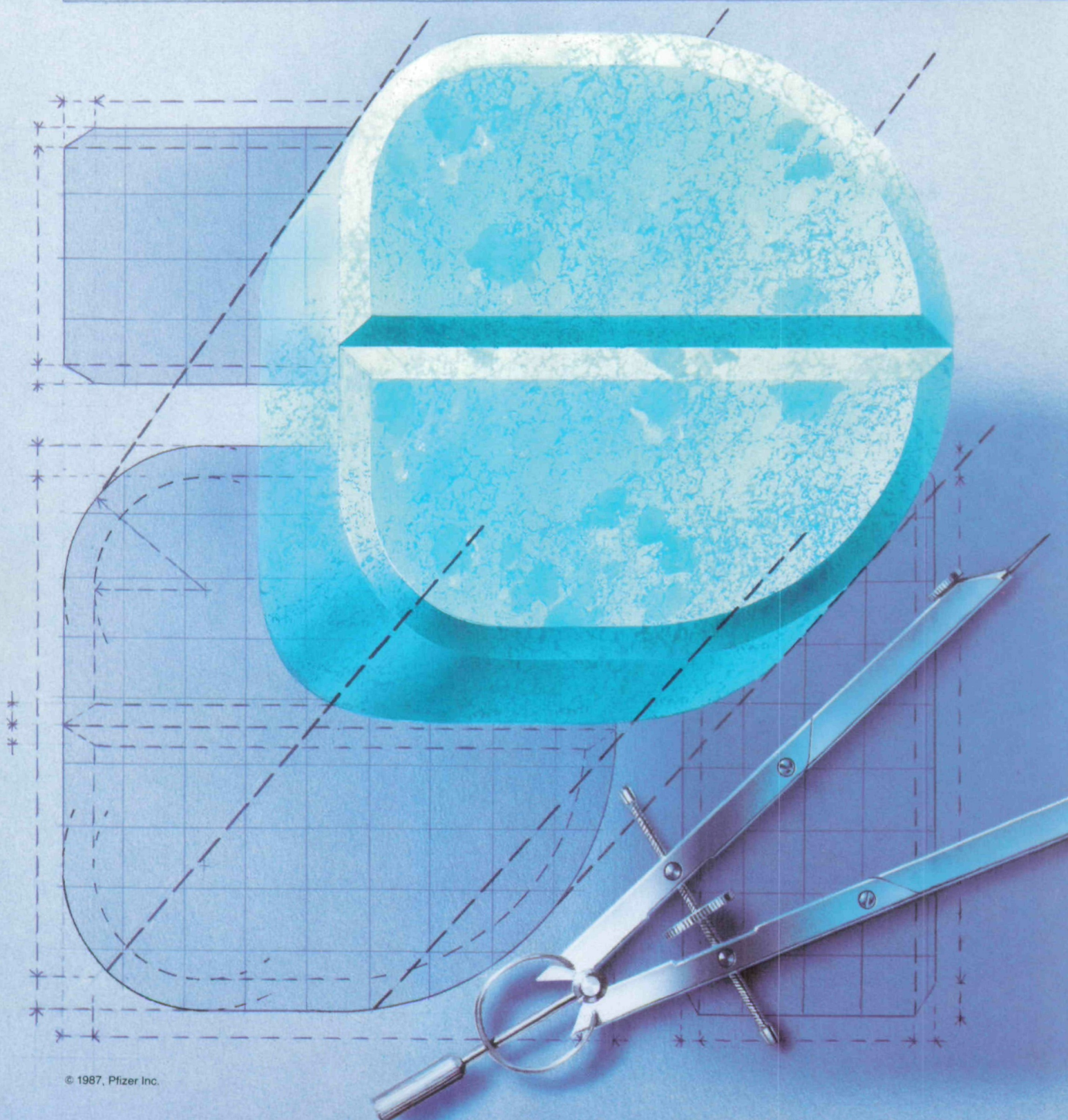
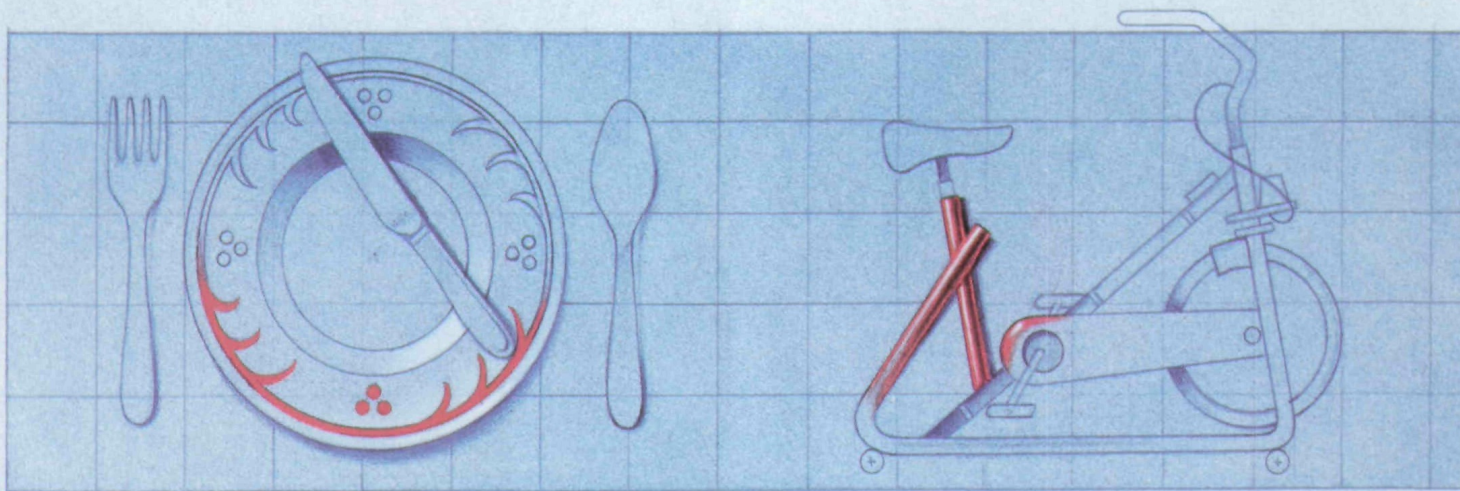
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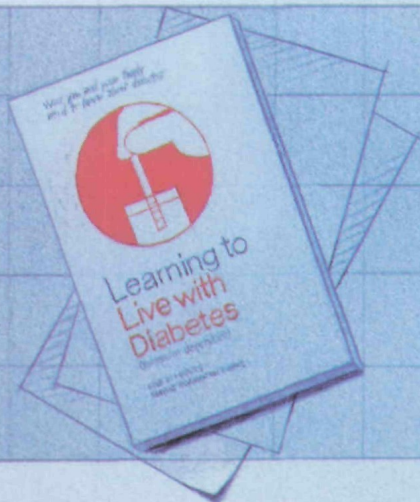
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1 D.A.W.

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A GENERATION AHEAD IN NIDDM CONTROL

Reference: 1. Clarke BF: Comparative effectiveness of glyburide in the treatment of non-insulin-dependent diabetes, in *Diagnosis and Management of Diabetes Mellitus*. Postgraduate Medicine: Custom Communications, April 1982, pp 57-65.

Please see Diabinese® (chlorpropamide) brief summary on the following page.

Pfizer LABORATORIES DIVISION
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BRIEF SUMMARY
DIABINESE® (chlorpropamide)
TABLETS, USP

CONTRAINDICATIONS

DIABINESE is contraindicated in patients with:
 1. Known hypersensitivity to the drug.
 2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes, 19 (supp. 2):747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of DIABINESE (chlorpropamide) and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS

General

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may cause elevated blood levels of DIABINESE and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Because of the long half-life of chlorpropamide, patients who become hypoglycemic during therapy require careful supervision of the dose and frequent feedings for at least 3 to 5 days. Hospitalization and intravenous glucose may be necessary.

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue DIABINESE (chlorpropamide) and administer insulin.

The effectiveness of any oral hypoglycemic drug, including DIABINESE, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given.

ADVERSE REACTIONS

Hypoglycemia: See PRECAUTIONS section.

Gastrointestinal Reactions: Cholestatic jaundice may occur rarely; DIABINESE should be discontinued if this occurs. Gastrointestinal disturbances are the most common reactions; nausea has been reported in less than 5% of patients, and diarrhea, vomiting, anorexia, and hunger in less than 2%. Other gastrointestinal disturbances have occurred in less than 1% of patients including proctocolitis. They tend to be dose related and may disappear when dosage is reduced.

Dermatologic Reactions: Pruritus has been reported in less than 3% of patients. Other allergic skin reactions, e.g., urticaria and maculopapular eruptions have been reported in approximately 1% or less of patients. These may be transient and may disappear despite continued use of DIABINESE (chlorpropamide); if skin reactions persist the drug should be discontinued.

Porphyrria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas. Skin eruptions rarely progressing to erythema multiforme and exfoliative dermatitis have also been reported.

Hematologic Reactions: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, pancytopenia, and eosinophilia have been reported with sulfonylureas.

Metabolic Reactions: Hepatic porphyria and disulfiram-like reactions have been reported with DIABINESE.

Endocrine Reactions: On rare occasions, chlorpropamide has caused a reaction identical to the syndrome of inappropriate antidiuretic hormone (ADH) secretion. The features of this syndrome result from excessive water retention and include hyponatremia, low serum osmolality, and high urine osmolality.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with DIABINESE or any other hypoglycemic agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, and to detect secondary failure. Glycosylated hemoglobin levels may also be of value in monitoring the patient's response to therapy.

The total daily dosage is generally taken at a single time each morning with breakfast. Occasionally cases of gastrointestinal intolerance may be relieved by dividing the daily dosage. A LOADING OR PRIMING DOSE IS NOT NECESSARY AND SHOULD NOT BE USED.

Initial Therapy: 1. The mild to moderately severe, middle-aged, stable, non-insulin-dependent diabetic patient should be started on 250 mg daily. Older patients should be started on smaller amounts of DIABINESE (chlorpropamide), in the range of 100 to 125 mg daily.

2. No transition period is necessary when transferring patients from other oral hypoglycemic agents to DIABINESE. The other agent may be discontinued abruptly and chlorpropamide started at once. In prescribing chlorpropamide, due consideration must be given to its greater potency.

Many mild to moderately severe, middle-aged, stable non-insulin-dependent diabetic patients receiving insulin can be placed directly on the oral drug and their insulin abruptly discontinued. For patients requiring more than 40 units of insulin daily, therapy with DIABINESE may be initiated with a 50 per cent reduction in insulin for the first few days, with subsequent further reductions dependent upon the response.

Five to seven days after the initial therapy, the blood level of chlorpropamide reaches a plateau. Dosage may subsequently be adjusted upward or downward by increments of not more than 50 to 125 mg at intervals of 3 to 5 days to obtain optimal control. More frequent adjustments are usually undesirable.

Maintenance Therapy: Most moderately severe, middle-aged, stable non-insulin-dependent diabetic patients are controlled by approximately 250 mg daily. Many investigators have found that some milder diabetics do well on daily doses of 100 mg or less. Many of the more severe diabetics may require 500 mg daily for adequate control. PATIENTS WHO DO NOT RESPOND COMPLETELY TO 500 MG DAILY WILL USUALLY NOT RESPOND TO HIGHER DOSES. MAINTENANCE DOSES ABOVE 750 MG DAILY SHOULD BE AVOIDED.

HOW SUPPLIED

Blue, "D"-shaped, scored tablets in strengths of 100 mg, tablet code 393; (100's, NDC #0663-3930-66; 500's, NDC #0663-3930-73; and 100 unit dose of 10 X 10, NDC #0663-3930-41) and 250 mg, tablet code 394; (100's, NDC #0663-3940-66; 250's, NDC #0663-3940-71; 1000's, NDC #0663-3940-82; 100 unit dose of 10 X 10, NDC #0663-3940-41; and 30's D-Pak, NDC #0663-3940-30).

RECOMMENDED STORAGE: Store below 86°F (30°C).

CAUTION: Federal law prohibits dispensing without prescription.



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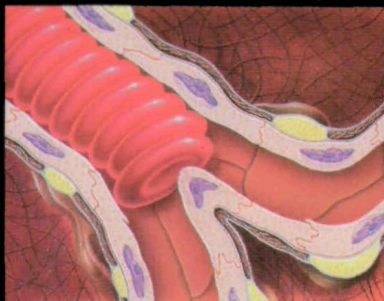
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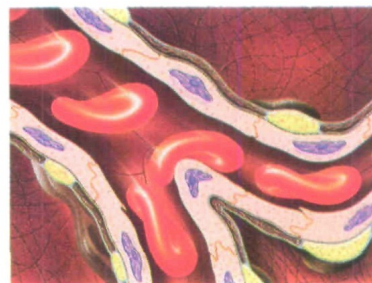
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Please see following page for references and brief summary of prescribing information.

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References: 1. Oughton J, et al: Diabetes mellitus: Its effect on the flow properties of blood. *Horm Metab Res* 11 (Suppl):112-129, 1981. 2. Schubotz R: Double-blind trial of pentoxifylline in diabetes with peripheral vascular disorders. *Pharmatherapeutica* 1(3):172-179, 1976. 3. Dormandy JA, et al: Clinical, hemodynamic, rheological, and biochemical findings in 126 patients with intermittent claudication. *Br Med J* 4: 576, 1973. 4. Reid HL, et al: Impaired red cell deformability in peripheral vascular disease. *Lancet* 1: 666, 1967. 5. Stormer B, et al: Rheological changes in the blood of patients with chronic arterial occlusive disease after the administration of vasoactive drugs. *Curr Med Res Opin* 4: 588, 1977. 6. Ehrly AM: Effects of orally administered pentoxifylline on muscular oxygen pressure in patients with intermittent claudication. *IRCS Med Sci* 10: 401, 1982.

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CONTRAINDICATIONS:

Trental® (pentoxifylline) should not be used 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. Trental® (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 Trental® (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.

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 Trental® (pentoxifylline) with and without anticoagulants or platelet aggregation inhibitors. Patients on warfarin should have more frequent monitoring of prothrombin time, 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. Trental® (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 Trental® (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 and 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 approximately 24 times (570 mg/kg) the maximum recommended human daily dose (MRHD) of 24 mg/kg for 18 months in mice and 18 months in rats with an additional 6 months without drug exposure in the latter. No carcinogenic potential for pentoxifylline was noted in the mouse study. In the rat study, there was a statistically significant increase in benign mammary fibroadenomas in females in the high dose group (24 X MRHD). The relevance of this finding to human use is uncertain since this was only a marginal statistically significant increase for a tumor that is common in aged rats. Pentoxifylline was devoid of mutagenic activity in various strains of *Salmonella* (Ames test) when tested in the presence and absence of metabolic activation.

Pregnancy: Category C. Teratogenic studies have been performed in rats and rabbits at oral doses up to about 25 and 10 times the maximum recommended human daily dose (MRHD) of 24 mg/kg, respectively. No evidence of fetal malformation was observed. Increased resorption was seen in rats at 25 times MRHD. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Trental® (pentoxifylline) should be used during pregnancy only if clearly needed.

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 children below the age of 18 years have not been established.

ADVERSE REACTIONS:

Clinical trials were conducted using either controlled-release Trental® (pentoxifylline) tablets for up to 60 weeks or immediate-release Trental® (pentoxifylline) capsules for up to 24 weeks. Dosage ranges in the tablet studies were 400 mg bid to tid and in the capsule studies, 200-400 mg tid.

The table summarizes the incidence (in percent) of adverse reactions considered drug related, as well as the numbers of patients who received controlled-

release Trental® (pentoxifylline) tablets, immediate-release Trental® (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 controlled-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

	Controlled-Release Tablets		Immediate-Release Capsules	
	Trental®	Placebo	Trental®	Placebo
(Numbers 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

Trental® (pentoxifylline) has 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; Respiratory—epistaxis, flu-like symptoms, laryngitis, nasal congestion; Skin and Appendages—brittle fingernails, pruritus, rash, urticaria; Special Senses—blurred vision, conjunctivitis, earache, scotoma; and 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; Digestive—hepatitis, jaundice; and Hematologic and Lymphatic—decreased serum fibrinogen, pancytopenia, purpura, thrombocytopenia.

OVERDOSAGE:

Overdosage with Trental® (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 adsorb pentoxifylline in patients who have overdosed.

DOSAGE AND ADMINISTRATION:

The usual dosage of Trental® (pentoxifylline) in controlled-release tablet form is one tablet (400 mg) three times a day with meals.

While the effect of Trental® (pentoxifylline) may be seen within 2 to 4 weeks, it is recommended that treatment be continued for at least 8 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 side 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 Trental® (pentoxifylline) should be discontinued.

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