NOVEMBER 1985 VOLUME 34 NUMBER 11

diabetes

A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION®

ORIGINAL CONTRIBUTIONS

RAPID PUBLICATION

DIAEAZ 34(11) 1071–1215 (1985)
ISSN 0012-1797

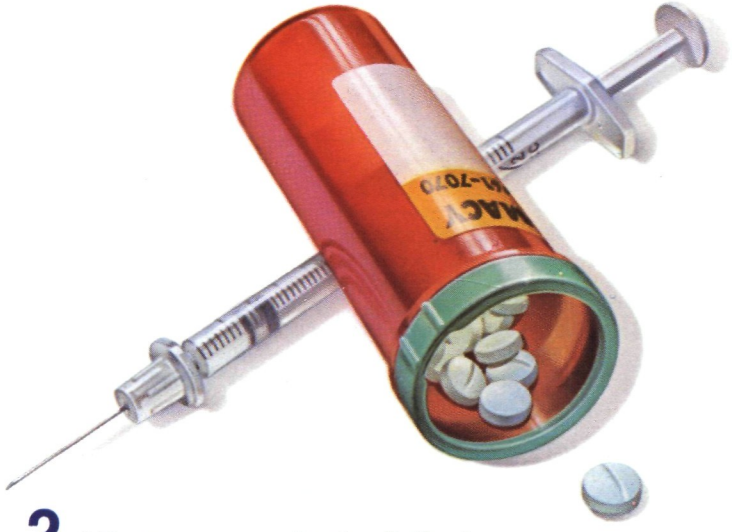
When a type II diabetic patient needs more than diet, unique MICRONASE® Tablets (glyburide) are a logical first choice.

Choosing antidiabetic

1. Micronase—a rational choice in type II diabetes

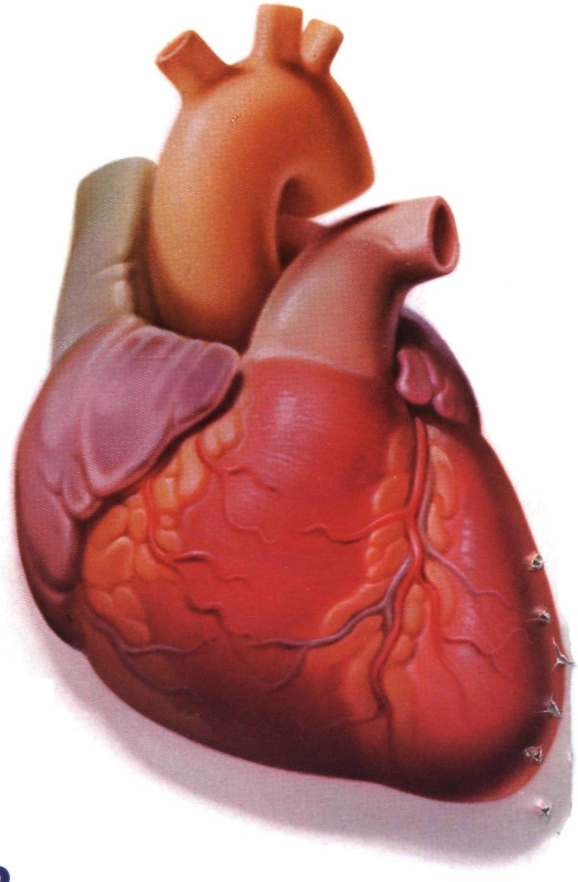
Insulin levels are normal or elevated in most patients with type II diabetes, although insulin action is markedly impaired. MICRONASE helps normalize the tissue response to endogenous insulin.

Initially, MICRONASE helps lower serum glucose in responsive patients by stimulating the release of additional insulin. As therapy continues, MICRONASE is believed to promote peripheral glucose metabolism by helping to correct defects at the cellular receptor and postreceptor levels.



2. Micronase—a single, daily dose provides 24-hour glycemic control

MICRONASE provides 24-hour control of blood glucose with a single, daily, low-milligram dose. MICRONASE may be taken with food, since food intake does not appear to affect its bioavailability.



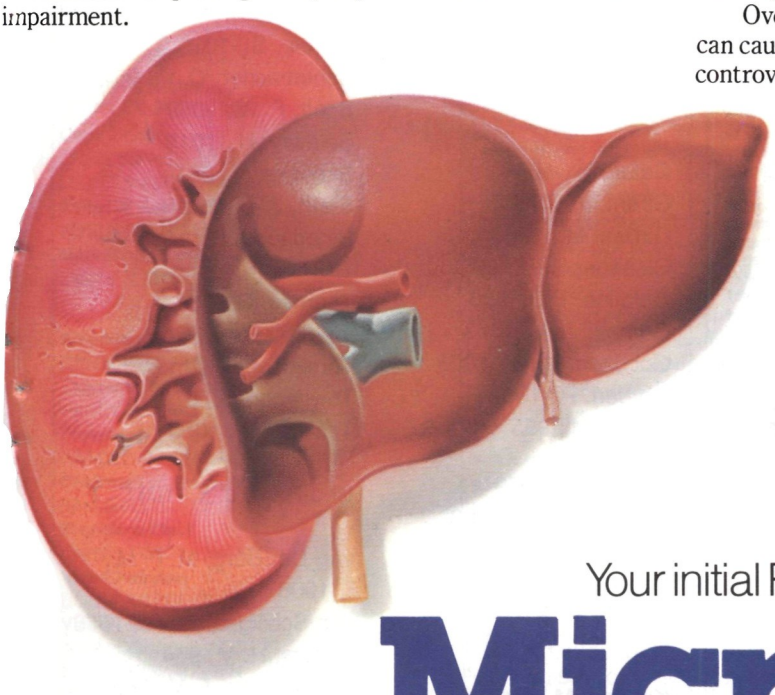
3. Micronase—for the type II diabetic patient who is also hypertensive: Control without risk of water retention

This may also be significant for the type II diabetic patier with congestive heart failure. MICRONASE actually causes mild diuresis.

therapy today

4. Micronase—an important consideration in the type II diabetic patient with renal impairment: Control plus unique dual excretion... 50% urine, 50% bile

Elimination of MICRONASE equally in bile and urine reduces the risk of drug accumulation, which may result in hypoglycemia. MICRONASE should be used with caution in patients with renal impairment; however, in a single-dose study, plasma clearance of MICRONASE was prolonged only in patients with severe renal impairment.



5. Micronase—for the patient who fails on other diabetic therapy: Potency and dosage flexibility

MICRONASE may prove effective when other drugs fail. Five mg of MICRONASE is approximately equivalent to 250 mg of chlorpropamide or 500 mg of acetohexamide in its ability to lower blood glucose. The dosage range of MICRONASE allows for greater dosage flexibility than other agents.

Overdosage of sulfonylureas, including MICRONASE, can cause hypoglycemia. Although the interpretations are controversial, the UGDP study reported in 1970 that the use of tolbutamide, an oral hypoglycemic drug, was associated with increased cardiovascular mortality.

Upjohn The Upjohn Company
Kalamazoo, MI 49001

Your initial Rx in type II diabetes

Micronase®

glyburide, 5 mg Tablets

For brief summary of prescribing information, please turn page.

NOVEMBER AUTHOR INDEX

(Volume 34, Number 11)

diabetes

A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION®

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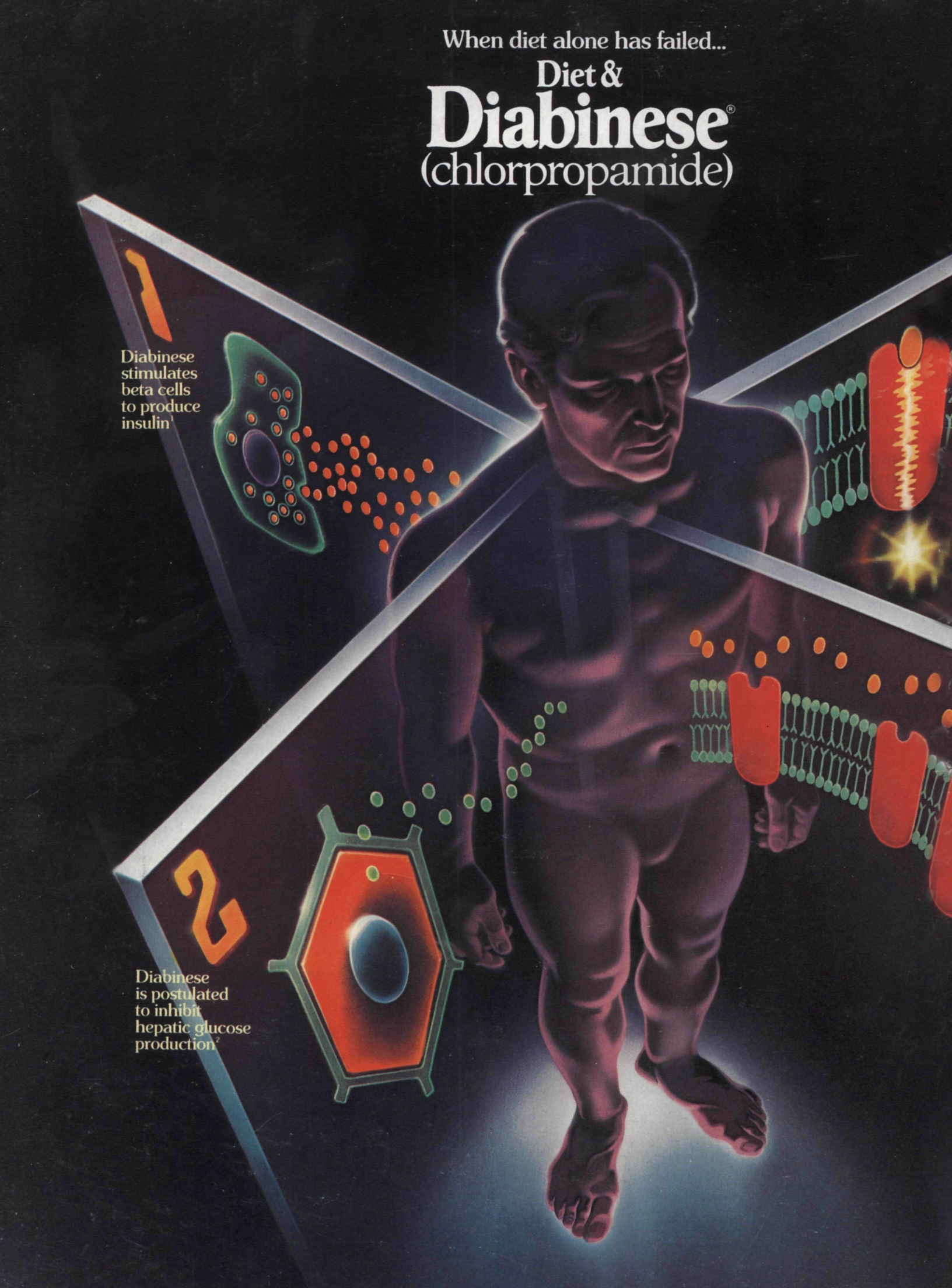
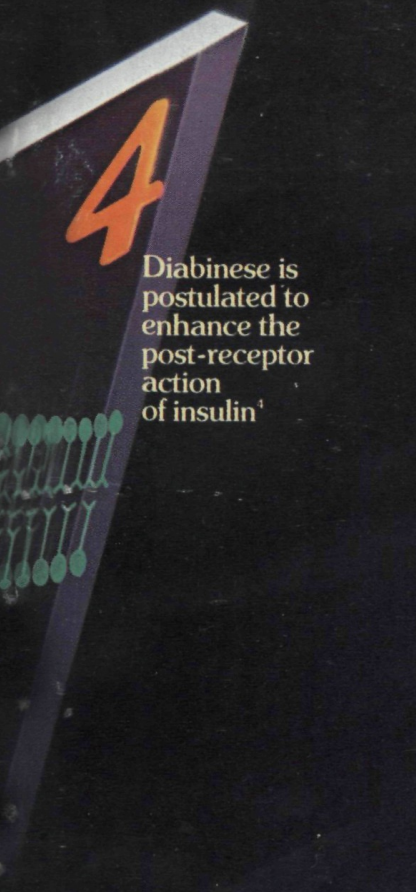


Acts on the defects in NIDDM



Diabinese is postulated to enhance the post-receptor action of insulin[4]

Today's research has identified four factors that contribute to hyperglycemia in NIDDM, and attributes to Diabinese (chlorpropamide) four possible mechanisms of control.

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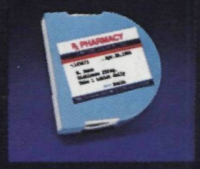

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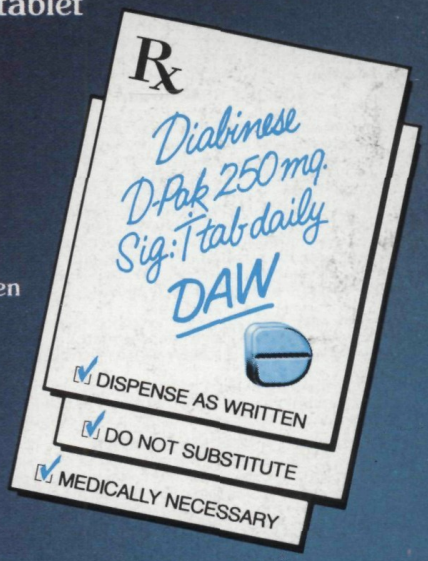
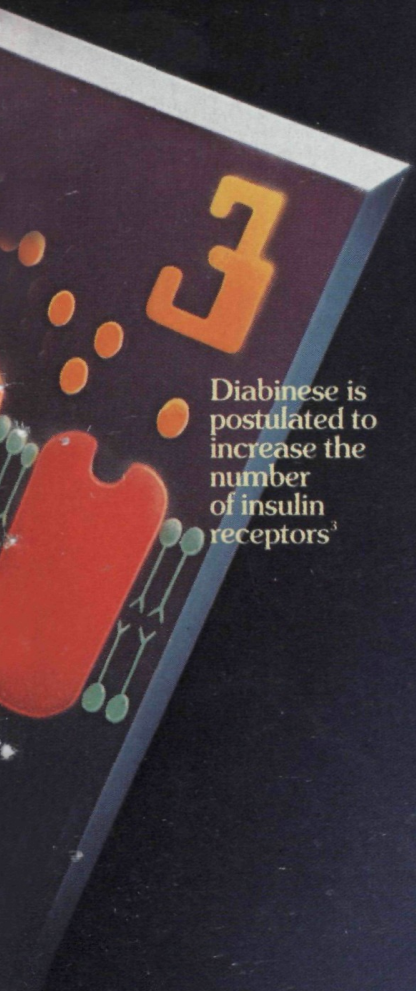


*When choosing a therapeutic regimen to treat non-insulin-dependent diabetes mellitus (NIDDM), many factors should be considered, including the patient's age, mental state, concomitant medication, and illnesses. As with all sulfonylureas, hypoglycemia may occur with Diabinese.



Diabinese is postulated to increase the number of insulin receptors[3]

Diet & Diabinese® (chlorpropamide)

Tablets, USP
100 mg, 250 mg
and D-Pak

The state of the art in oral diabetic therapy

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

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References: 1. Judzewitsch RG, Pfeifer MA, Best JD: Chronic chlorpropamide therapy of non-insulin-dependent diabetes augments basal and stimulated insulin secretion by increasing islet sensitivity to glucose. *J Clin Endocrinol Metab* 55 (2):321-328, 1982. **2.** Best JD, Judzewitsch RG, Pfeifer MA: The effect of chronic sulfonylurea therapy on hepatic glucose production in non-insulin-dependent diabetes. *Diabetes* 31:333-338, 1982. **3.** Olefsky JM, Reaven GM: Effects of sulfonylurea therapy on insulin binding to mononuclear leukocytes of diabetic patients. *Am J Med* 60:89-95, 1976. **4.** Salhanick AI, Konowitz P, Amatruda JM: Potentiation of insulin action by a sulfonylurea in primary cultures of hepatocytes from normal and diabetic rats. *Diabetes* 32:206-212, 1983.

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 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 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; if skin reactions persist the drug should be discontinued.

Porphyria 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, 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 three to five 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.

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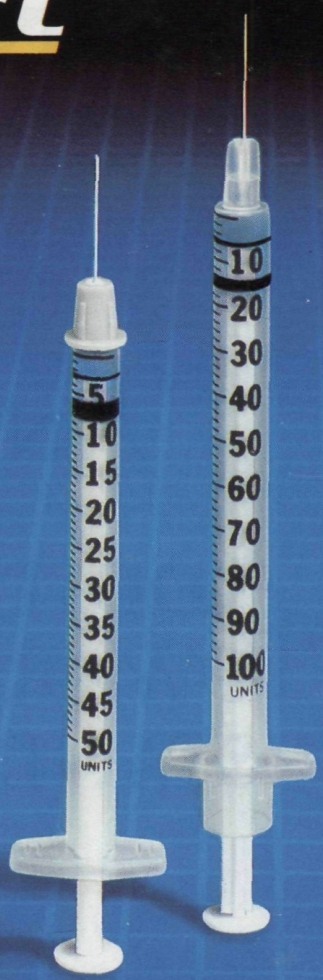

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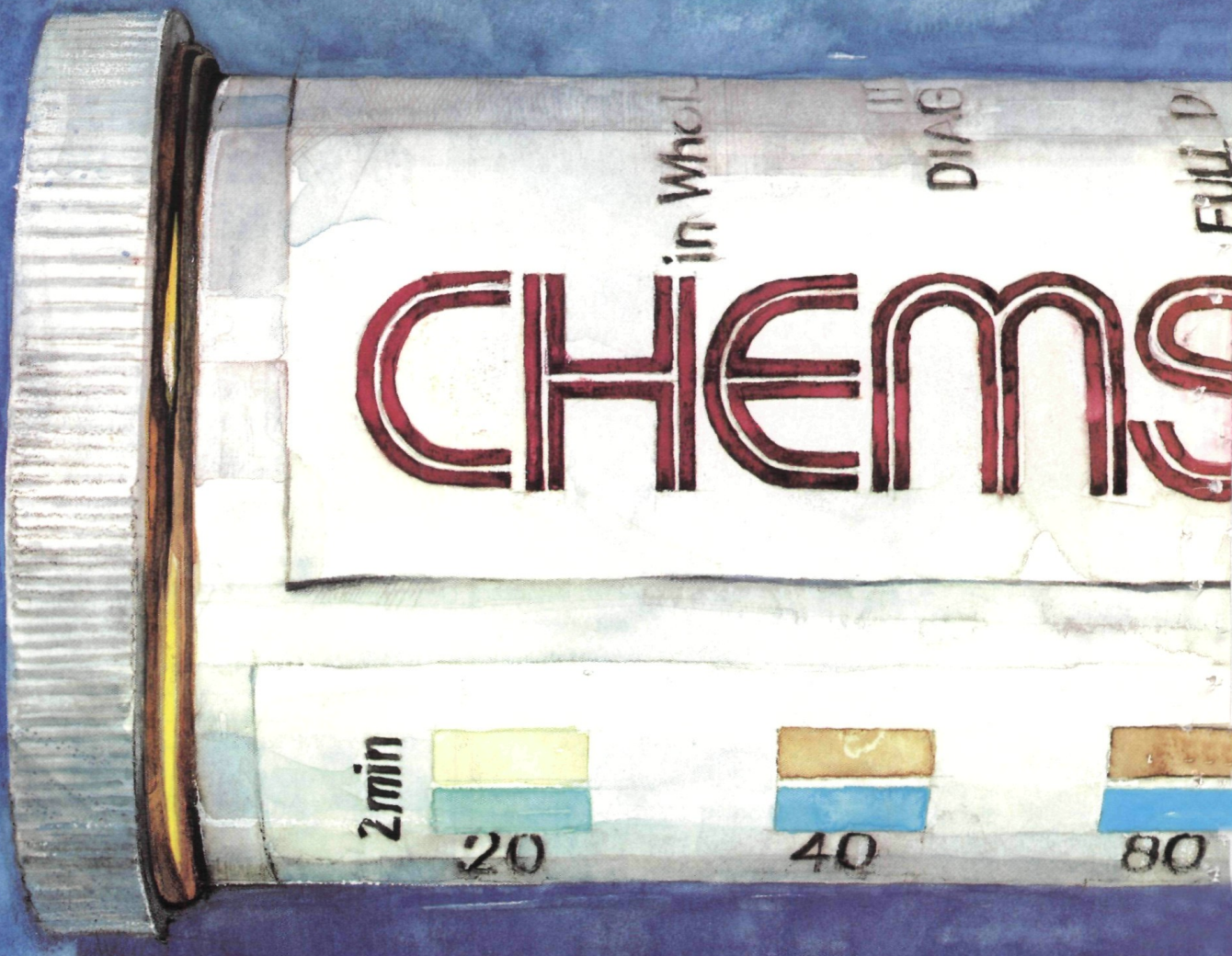

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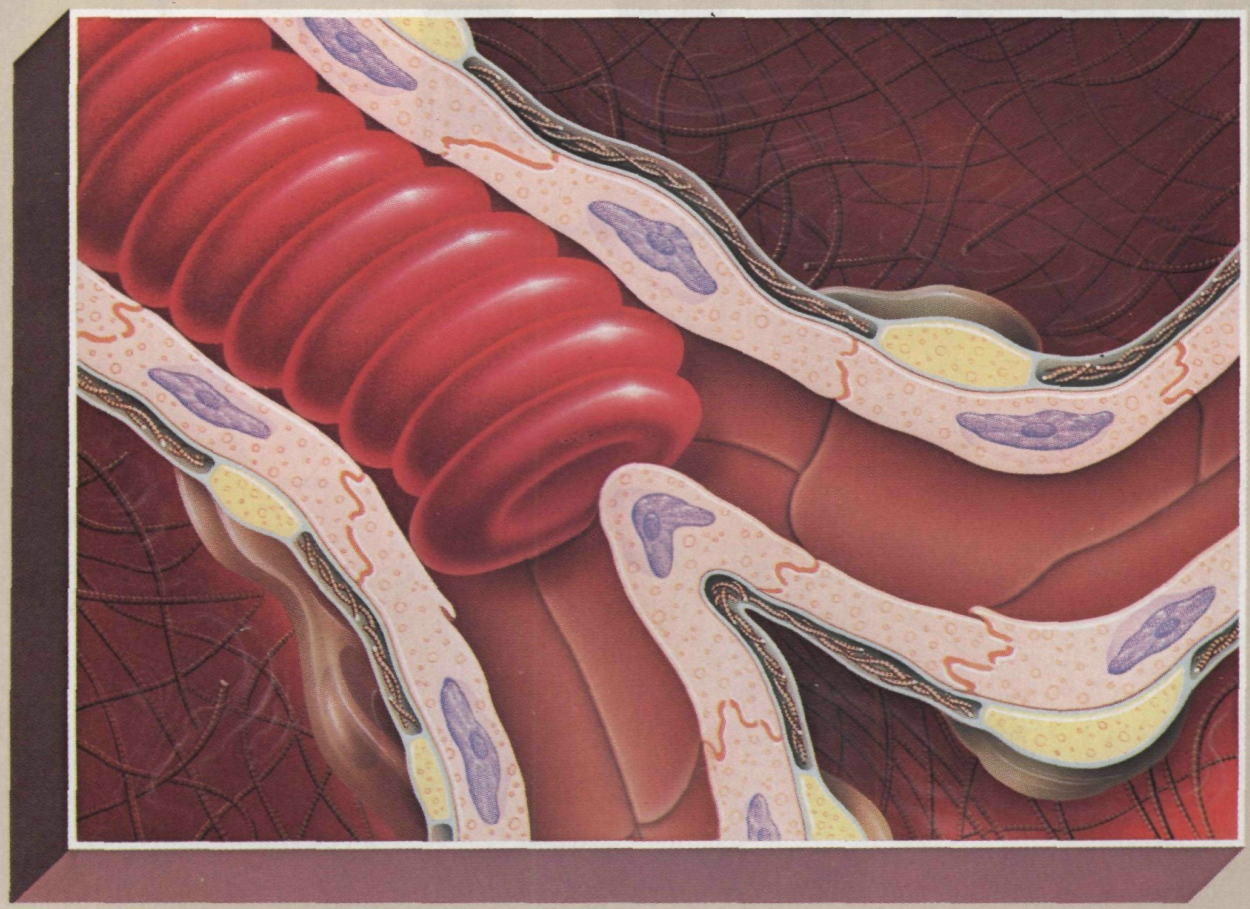
Why peripheral vasodilators fail to improve microcirculatory blood flow



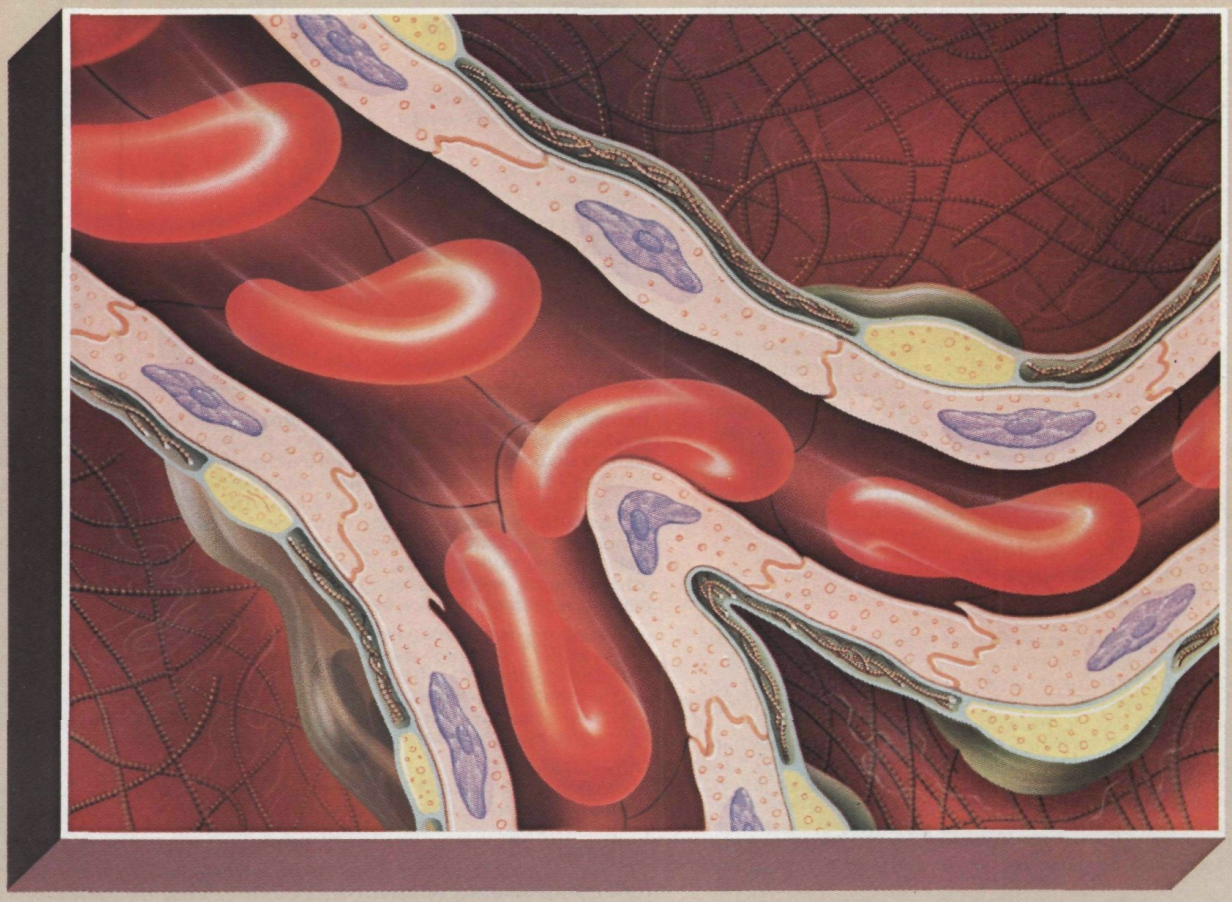
In chronic occlusive arterial disease, reduced blood flow downstream of a stenosis results in additional changes that further decrease efficient flow in the microcirculation.

Red blood cells become less flexible, impairing their normal capacity to pass through capillaries often less than half of the cells' diameter.[1] In addition, blood viscosity is increased.[2]

As flow through the microcirculation becomes more sluggish, acids and metabolites accumulate. Reduced tissue oxygenation results in painful claudication that limits the distance patients can walk.

Peripheral vasodilators cannot affect flow through arteries already maximally dilated, or through those with fixed stenoses. In addition, these agents do not increase the flexibility of red cells or decrease blood viscosity. Microcirculatory blood flow and tissue oxygenation do not improve.

...and how only Trental® succeeds.
(pentoxifylline)



Improves red blood cell flexibility

Trental® is not a vasodilator, not an anticoagulant, and not related to aspirin or dipyridamole. Trental® increases the flexibility of red cells, thereby improving their capacity to pass through capillaries. Blood viscosity is also reduced, decreasing resistance and improving perfusion of the ischemic microcirculation. As a result, tissue oxygenation is increased.

Trental® has been shown to significantly increase oxygenation in the calf muscles of patients with intermittent claudication.[3]

Well tolerated

Side effects with Trental® are usually mild, transient, and generally confined to reversible CNS or GI effects.

Trental® is compatible for concurrent use with antihypertensive, beta-blocker, digitalis, diuretic, antidiabetic, and antiarrhythmic regimens. (See full prescribing information.)

While the clinical benefits of Trental® may be seen within two to four weeks, it is recommended that treatment be continued for at least eight weeks. To maintain clinical benefit, continued therapy is necessary.

The usual dose of Trental® is one 400-mg tablet taken three times a day with meals.

Trental®
(pentoxifylline) 400 mg Tablets

The first proven-effective agent for intermittent claudication

Trental® can improve function and symptoms but is not intended to replace more definitive therapy such as surgery.

See following page for references and brief summary of prescribing information.

References:
1. Reid HL, et al: Impaired red cell deformability in peripheral vascular disease. *Lancet 1*:666-667, 1967.
2. Dormandy JA, et al: Clinical, haemodynamic, rheological, and biochemical findings in 126 patients with intermittent claudication. *Br Med J 4*:576-581, 1973.
3. Ehrly AM: Effects of orally administered pentoxifylline on muscular oxygen pressure in patients with intermittent claudication. *IRCS Med Sci 10*:401-402, 1982.

Trental® (pentoxifylline) Tablets, 400 mg

A brief summary of the Prescribing Information follows.

INDICATIONS AND USAGE:
Trental® (pentoxifylline) is indicated for the treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs. Trental® (pentoxifylline) 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:
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 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. 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 Hemic 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.

Hoechst-Roussel Pharmaceuticals Inc.
Somerville, New Jersey 08876

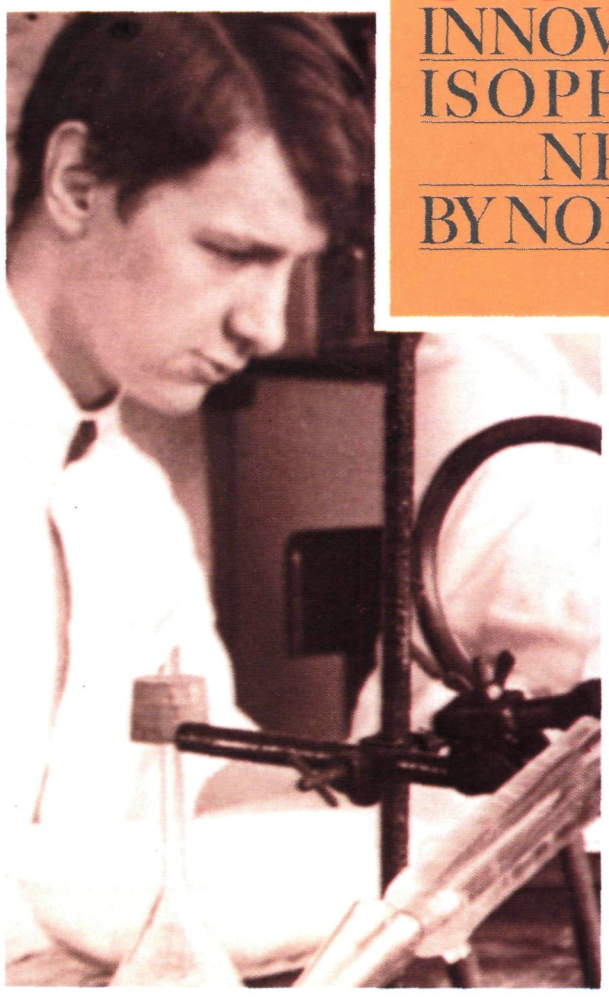
Hoechst

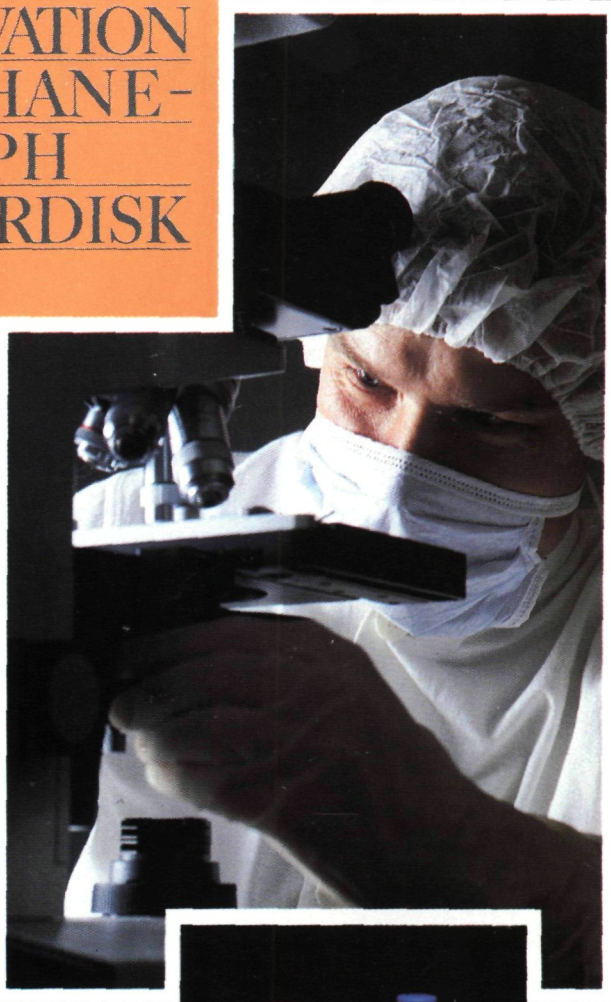
Trental®
(pentoxifylline)
TABLETS, 400 mg

The first proven-effective agent for intermittent claudication

Q7383-685

50 YEARS OF INNOVATION ISOPHANE-NPH BY NORDISK





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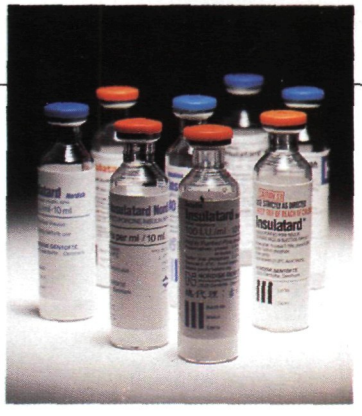

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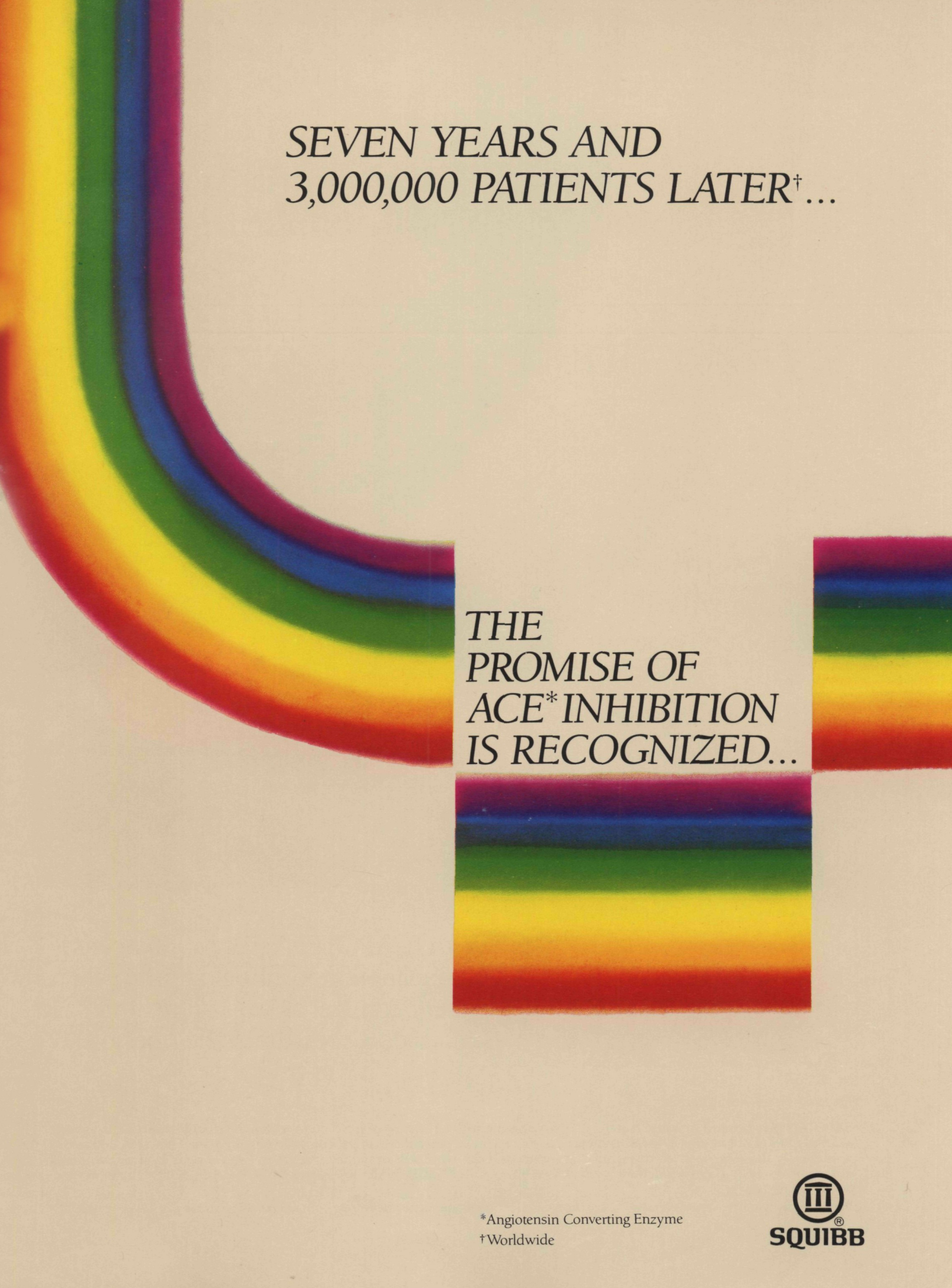
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3,000,000 PATIENTS LATER†...
THE
PROMISE OF
ACE* INHIBITION
IS RECOGNIZED...
*Angiotensin Converting Enzyme
†Worldwide
SQUIBB

"With [CAPOTEN® (captopril tablets)] it appears that for the first time ever a patient can feel as well on treatment for high blood pressure as he does off it."[1]

*Angiotensin Converting Enzyme

†CAPOTEN may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

‡The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited

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ACE*INHIBITOR

CAPOTEN®

captopril tablets

HELP PUT QUALITY BACK INTO LIVING

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension — CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Neutropenia/Agranulocytosis — Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine <1.6 mg/dL and no collagen disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria — Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension — Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension — Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure — About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* — A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

Surgery/Anesthesia — If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy* — Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 houn after the initial dose.

Agents Having Vasodilator Activity — In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release — Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity — The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium — Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis — Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C — There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal — About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic — Neutropenia/agranulocytosis have occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic — Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients — reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular — Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia — About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg also available in bottles of 1000), and in UNIMATIC® single dose packs of 100 tablets.
(J3-658C)

Reference:

1. Stumpe KO, Overlack A, Kolloch R, et al: Long-term efficacy of angiotensin-converting-enzyme inhibition with captopril in mild-to-moderate essential hypertension. Br J Clin Pharmacol 14(suppl 2):121S-126S, 1982.

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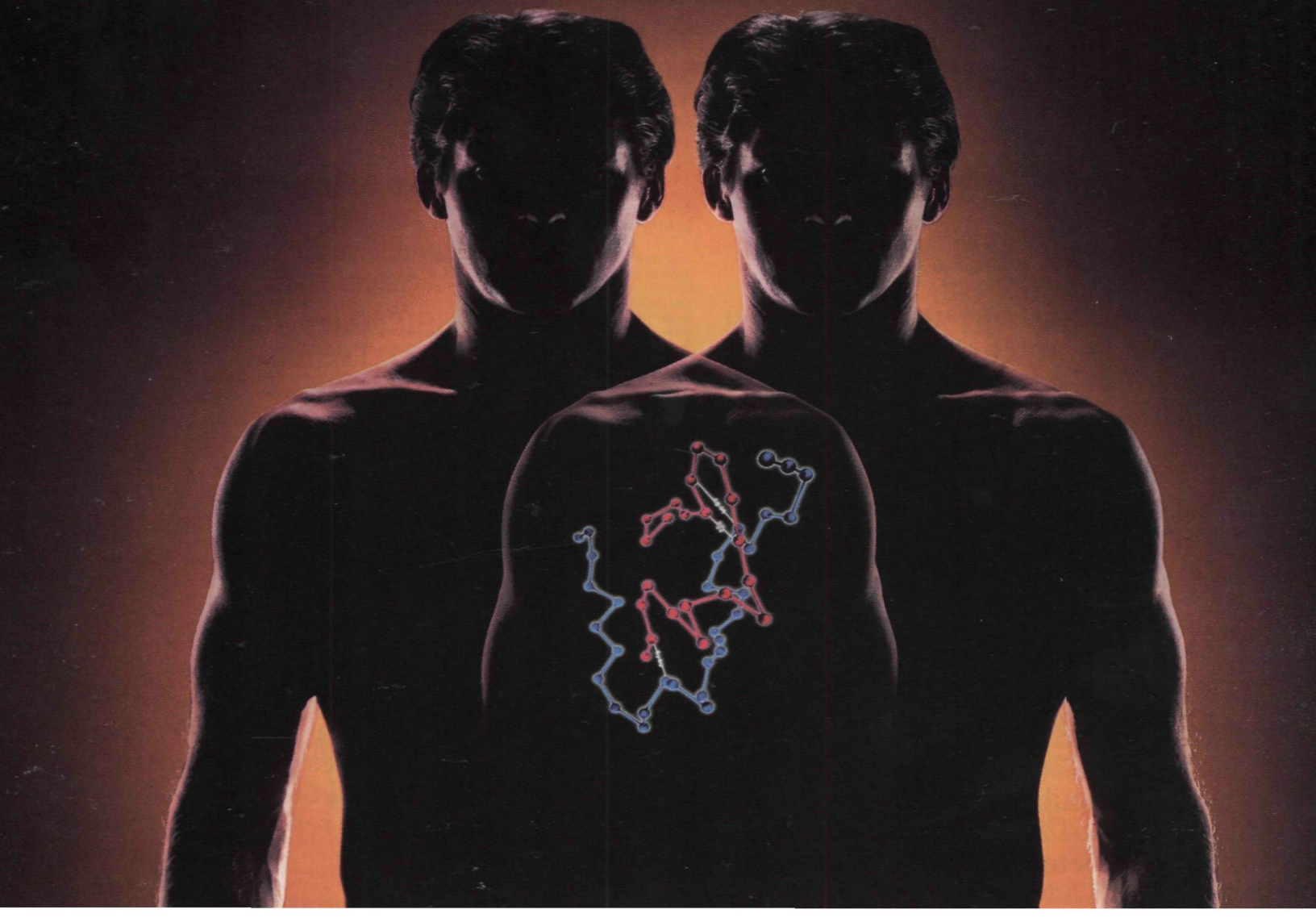

and it is identical to natural human insulin

From Lilly, a leader in diabetes care for six decades, there is now available the first and only insulin *not* derived from beef or pork pancreases—Humulin® (human insulin [recombinant DNA origin]).

In multicenter studies completed to date, Humulin was shown to be less immunogenic than mixed beef-pork or purified pork insulin. The clinical significance of these data has not yet been demonstrated.

Available in two forms: rapid-acting *Humulin® R* (regular human insulin [recombinant DNA origin], Injection) and intermediate-acting *Humulin® N* (NPH human insulin [recombinant DNA origin], Isophane Suspension).

Humulin®
human insulin
(recombinant DNA origin)

Lilly Leadership
IN DIABETES CARE

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN REFINEMENT, PURITY, STRENGTH, BRAND (MANUFACTURER), TYPE (REGULAR, NPH, LENTE®, ETC.), AND/OR METHOD OF MANUFACTURE (RECOMBINANT DNA VERSUS ANIMAL-SOURCE INSULIN) MAY RESULT IN THE NEED FOR A CHANGE IN DOSAGE.

For information on insulin delivery systems, contact CPI: 1-(800)-CARDIAC.

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