MAY 1985 VOLUME 34 NUMBER 5
PART 1 OF 2

diabetes

A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION®

ORIGINAL CONTRIBUTIONS

DIAEAZ 34(5) 415–520 (1985)
ISSN 0012-1797

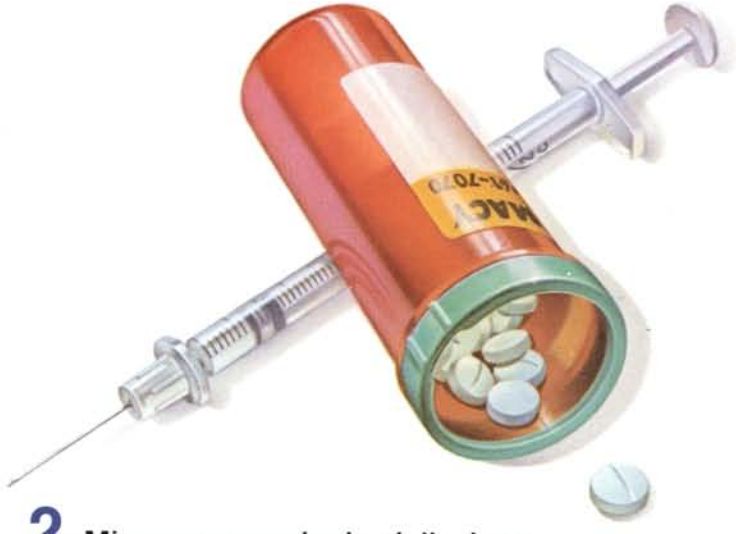
When a type II diabetic patient needs more than diet, unique MICRONASE® Tablets (glyburide) are a logical first choice.

Choosing antidiabetic

1. Micronase—a rational choice in type II diabetes

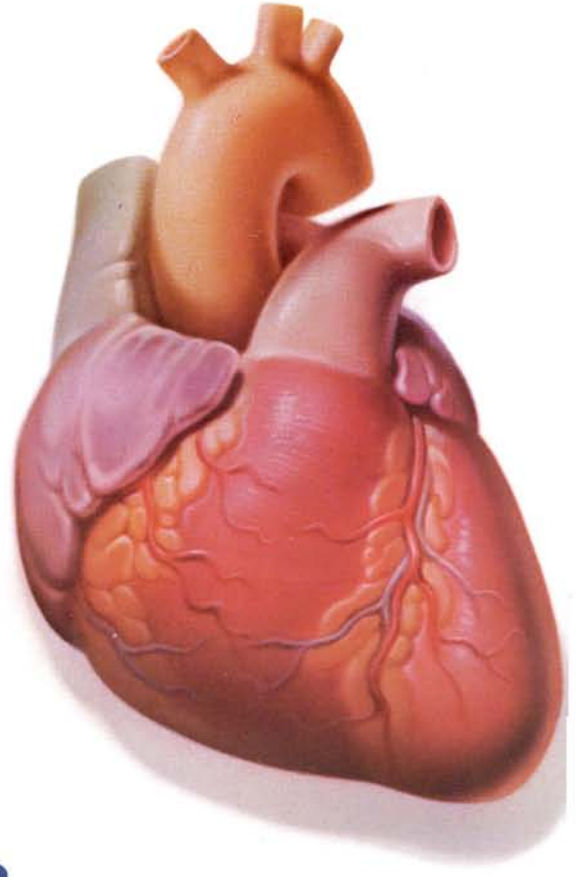
Insulin levels are normal or elevated in most patients with type II diabetes, although insulin action is markedly impaired. MICRONASE helps normalize the tissue response to endogenous insulin.

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.



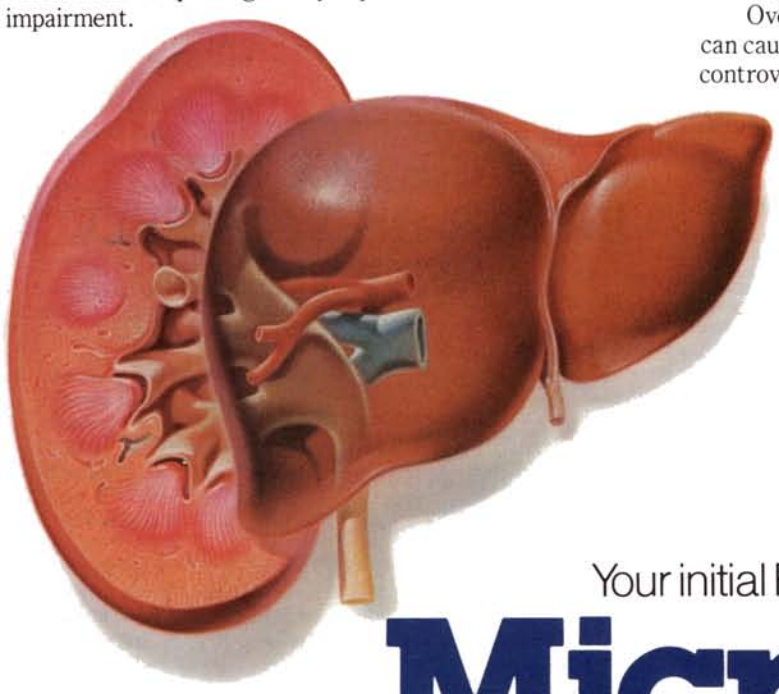
3. Micronase—for the type II diabetic patient who is also hypertensive: Control without risk of water retention

This may also be significant for the type II diabetic patient 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.

diabetes

A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION®

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Manuscripts should be typewritten, with double spacing, and submitted in triplicate together with three copies of figures and photomicrographs. Manuscripts prepared in accord with the requirements specified in the document, "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," Annals of Internal Medicine 1982; 96:766–71, will be considered for publication.

References should be presented in the style of the following examples and numbered in order of appearance in the text: For Periodicals—Banting, F. G., and Best, C. H.: The internal secretion of the pancreas. J. Lab. Clin. Med. 1922; 7:251–66. For Books—Allen, Frederick M.: Studies Concerning Glycosuria and Diabetes. Cambridge, Harvard University Press, 1913:461.

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ADVERTISING INFORMATION

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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 over-all 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.

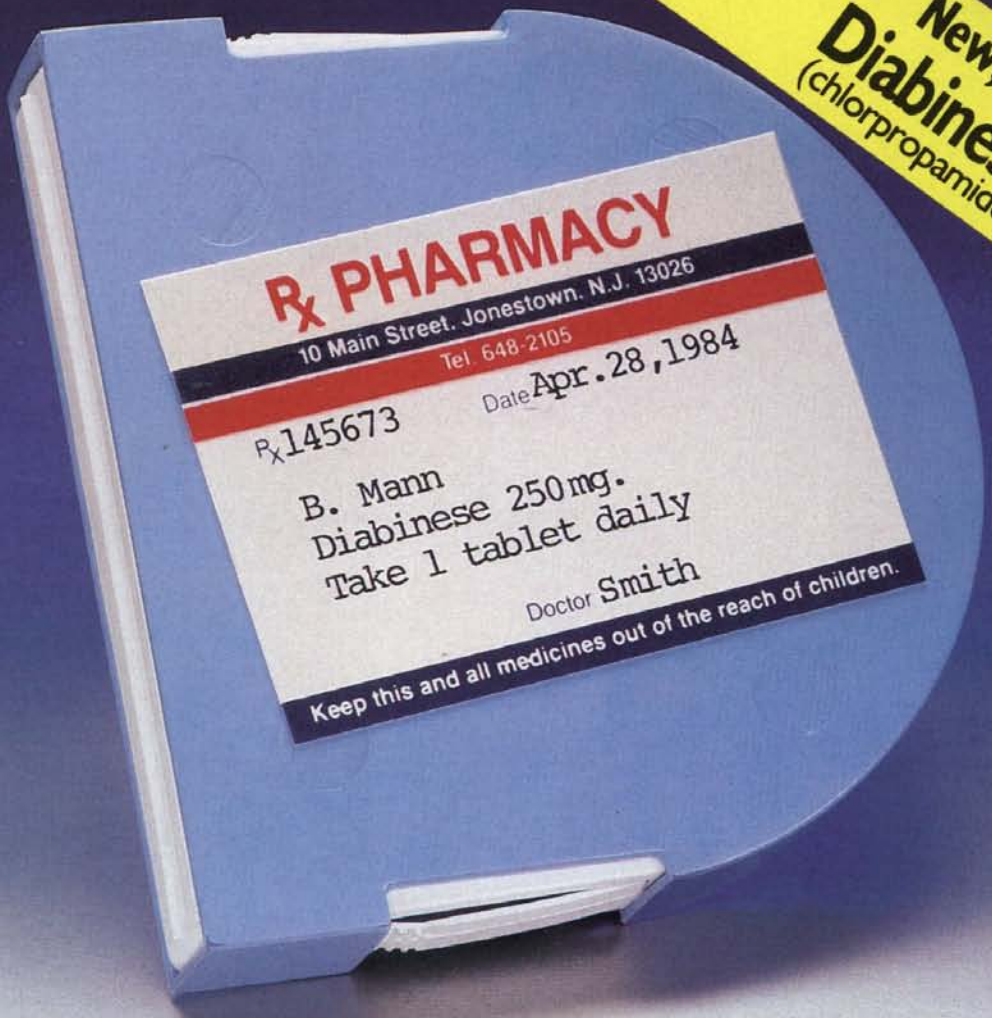
SUPPLY: Blue, 'D'-shaped, scored tablets in strengths of 100 mg, tablet code 393: (100's, NDC# 0663-3930-66; 500's, NDC# 0663-3930-73; and 100 unit dose of 10 x 10, NDC# 0663-3930-41) and 250 mg, tablet code 394; (100's, NDC# 0663-3940-66; 250's, NDC# 0663-3940-71; 1000's, NDC# 0663-3940-82; 100 unit dose of 10 x 10, NDC# 0663-3940-41; and 28's D-Pak, NDC# 0663-3940-28).

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

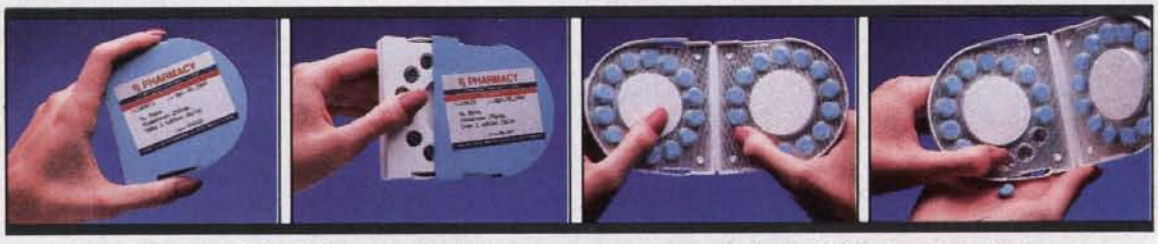
CAUTION: Federal law prohibits dispensing without prescription.

Pfizer
LABORATORIES DIVISION
PFIZER INC.

New, Improved
Diabinese® D-Pak
(chlorpropamide) Tablets 250 mg



The Case for Compliance



The Diabinese® (chlorpropamide) Tablets 250 mg D-Pak: A convenient way for patients to remember and keep track of every once-a-day dose. Now easier to use.

The Diabinese D-Pak (dispenser pack) contains a full 4-week supply of Diabinese 250-mg tablets in a lightweight, D-shaped, compact case. Inside, the distinctive blue, D-shaped tablets are arranged in easy-to-follow circles under clear day-of-the-week headings. So it is almost impossible to accidentally skip or repeat a dose. The blister packaging has been improved so tablets are easier to remove. The Diabinese D-Pak is particularly beneficial to the newly diagnosed NIDDM patient who is a dietary failure, since compliance with a new therapeutic regimen can be a problem.

Next time you prescribe Diabinese 250 mg *q.d.* specify the

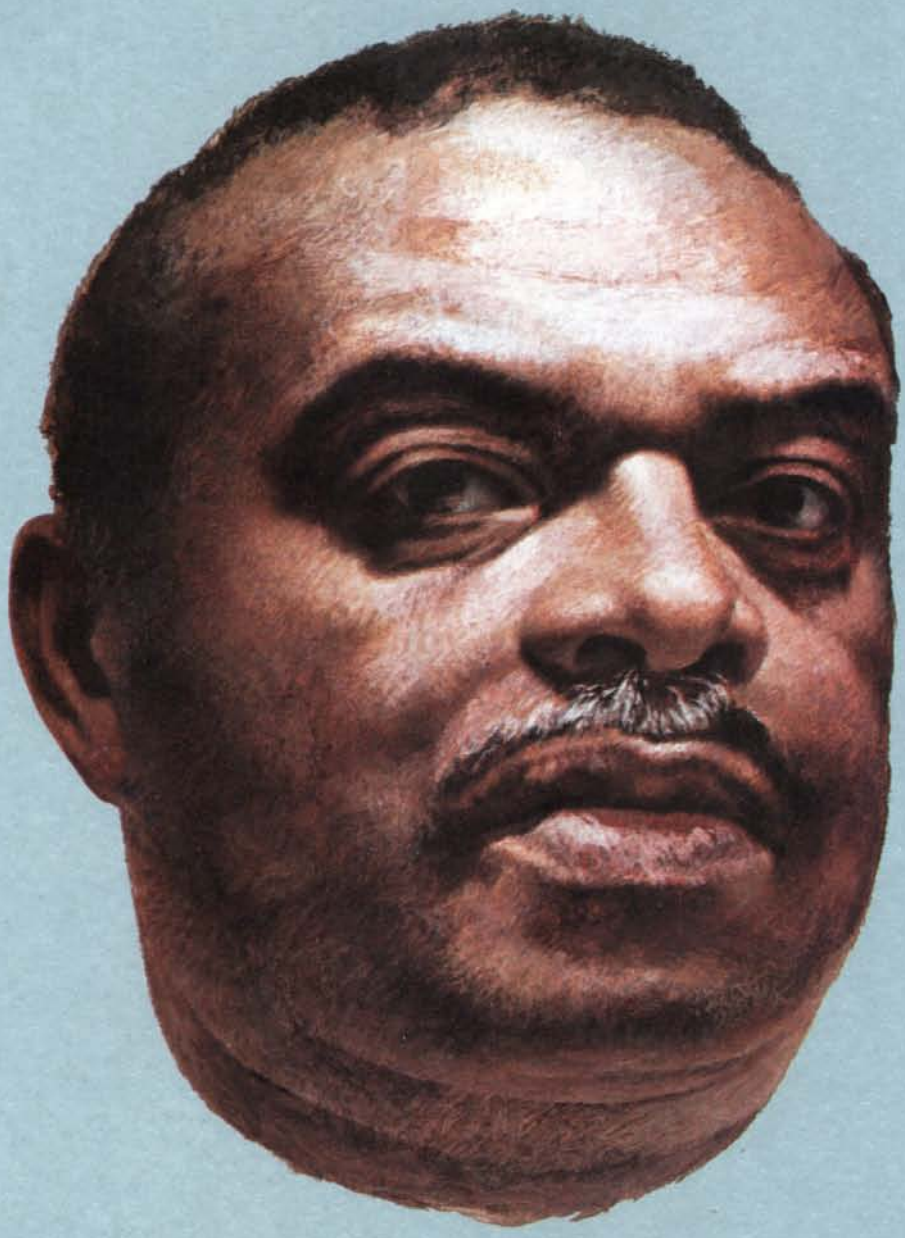
Diabinese® D-Pak
(chlorpropamide) Tablets 250 mg

Pfizer LABORATORIES DIVISION
PFIZER INC

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

BEHIND THE FACE OF HYPERTENSION

New evidence for central control



For the obese hypertensive

"Hyperactivity of the sympathetic nervous system may be a major factor in the pathogenesis of hypertension in obesity." [1]

Effective central control of blood pressure

Tablets of 0.1, 0.2, 0.3 mg

Catapres®
(clonidine HCl)

Hypertension

Please see last page for brief summary, including warnings, precautions, and adverse reactions.

BEHIND THE FACE OF HYPERTENSION

New evidence for central control

Catapres®
(clonidine HCl)
Hypertension

Catapres®

(clonidine hydrochloride)

Tablets of 0.1, 0.2, 0.3 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000 and unit dose package of 100. Also available as 0.3 mg (peach) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

Under license from Boehringer Ingelheim International GmbH

Reference:

1. Pioneering Research in Hypertension: The Role of the Sympathetic Nervous System, film and monograph, Boehringer Ingelheim Ltd., 1982.

BOEHRINGER INGELHEIM®
Boehringer Ingelheim

Boehringer Ingelheim Ltd.
Ridgefield, CT 06877

ANNOUNCES

THE FIRST SEMI-ANNUAL GRANTS TOWARD A BETTER UNDERSTANDING OF DIABETES

The Trustees of the Foundation are pleased to announce the funding of 10 special projects. Four grants have been awarded in basic research, three in clinical research and three in education.

Basic Research Grants:

Ronald W. Dudek, Ph.D.
East Carolina School of Medicine, Greenville, NC.
"Regeneration of Pancreatic Islets."

Renato N. Muscardo, M.D.
University of Connecticut School of Medicine
Newington, CT.
"Modulation of Endothelial Cell Response to Injury by Second Generation Sulfonylureas."

Carole Ober, Ph.D.
Northwestern University Medical School, Chicago, IL.
"An Investigation of the DNA Polymorphism Flanking the Insulin and Its Relationship to Gestational Onset Diabetes Mellitus."

Robert W. Rees-Jones, M.D.
Columbia University, College of Physicians and Surgeons, New York, NY.
"Identification of Islet Antigens to Which Auto-immunity is Directed in Type I Diabetes Mellitus."

Clinical Research Grants:

William T. Garrison, Ph.D.
Baystate Medical Center, Springfield, MA.
"Measuring the Coping Response to Early-Onset Diabetes Mellitus."

Julian J. Irias, M.D., Ida G. Braun, M.D. and
Arlee S. Maier, Ph.D.
Children's Hospital Medical Center of Northern California, Oakland, CA.
"Feasibility of Developing (a) Methods to Analyze the Role of Discrete Parental Cognitive Factors in the Home Management of Diabetic Children and (b) Intervention Strategies Based on this Analysis."

Robert S. Mecklenburg, M.D., FACP
The Mason Clinic, Seattle, WA.
"Computer Assisted Self Adjustment of Insulin Dose in Patients with Type I Diabetes Mellitus."

Education Grants:

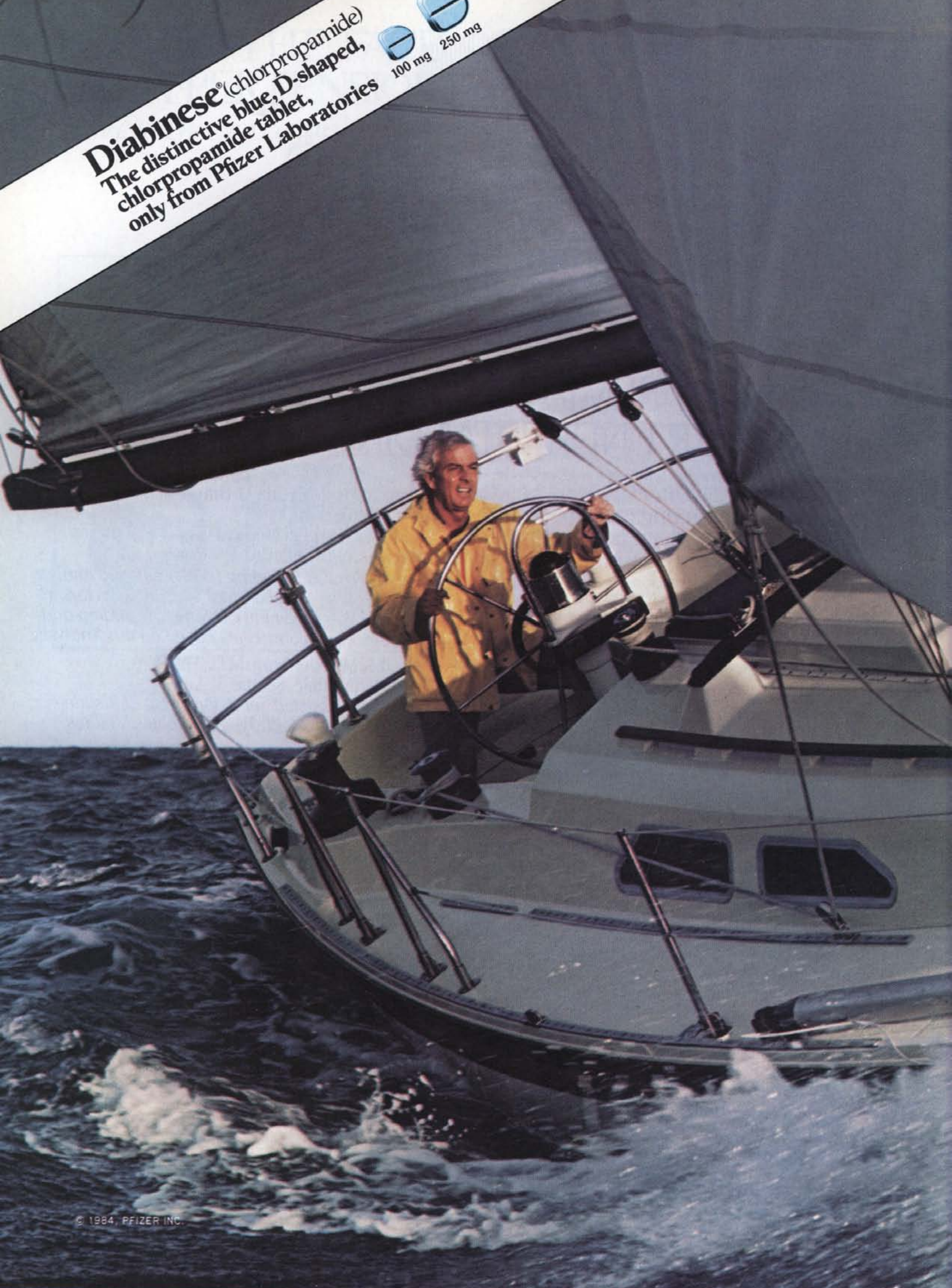
Gail D'Eramo, R.N., M.S.
Albert Einstein College of Medicine, Bronx, NY.
"Educational Approaches to Self Blood Glucose Monitoring in Obese Type II Diabetic Individuals."

J. Don Johnson, M.D.
Lamar Clinic, Memphis, TN.
"Home Based Education for the Newly Diagnosed and Potentially Non-Compliant Type II Diabetic Patient."

Rebecca Wiese, M.D.
Louisville Memorial Primary Care Center,
Louisville, KY.
"Analyzing Dietary Motivation and Changes in a Low Income Diabetic Population with the Use of Cooking Classes."

For further information on the Foundation, write to Herbert Rosenkilde, M.D., Executive Director, Diabetes Research and Education Foundation, Inc., P.O. Box 6168, Bridgewater, NJ 08807-9998.

Q6967-385


Diabinese® (chlorpropamide)
The distinctive blue, D-shaped, chlorpropamide tablet, only from Pfizer Laboratories
100 mg
250 mg
© 1984, PFIZER INC.

Holding Course...

for continued control of the NIDDM patient.

Control of blood sugar requires a day-to-day, week-to-week vigil, particularly when diet alone has failed in NIDDM. Once control has been successfully achieved with diet and Diabinese® (chlorpropamide), the logical course is to continue the regimen.

Diabinese is the most widely prescribed oral diabetic agent in the United States.

As with all sulfonylureas, hypoglycemia may occur with Diabinese, but less frequently than with insulin therapy.

Diabinese effectively controls hyperglycemia...

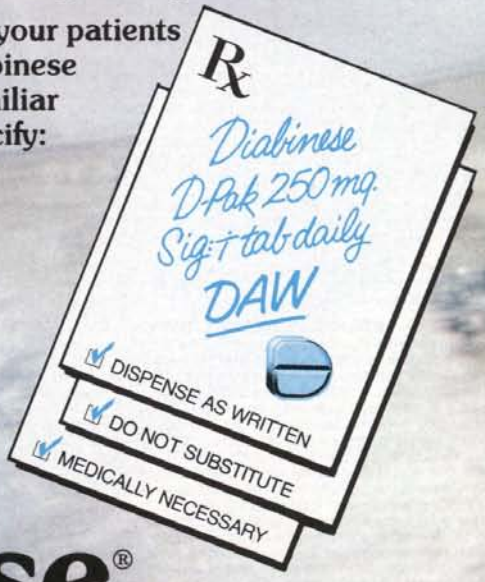
- known to stimulate beta cells to produce insulin[1,2]
- normalizes hepatic glucose production[2]
- postulated to increase the number of insulin receptors[3]
- postulated to enhance the postreceptor action of insulin[4]

The Diabinese D-Pak helps patients remember and keep track of the convenient once-a-day regimen... which encourages compliance.

To be sure your patients who are controlled on Diabinese continue to receive the familiar blue, D-shaped tablet, specify:

- *Do not substitute,*
- *Medically necessary,* or
- *Dispense as written,*

depending on the state in which you practice.



When diet alone fails...

Diet & Diabinese®

(chlorpropamide)

Tablets
100 mg, 250 mg
and D-Pak

A proven regimen...continue it with confidence.

Pfizer LABORATORIES DIVISION
PFIZER INC.

Leaders in Oral Diabetic Therapy

Please see references and Diabinese® Brief Summary on following page.

MAY AUTHOR INDEX

(Volume 34, Number 5)

AUTOMATED HbA_{1c} IS HERE!

Every 8 minutes after you push this button, you get a complete analysis.

If your laboratory performs 100 or more glycosylated hemoglobin analyses per week, you probably wish you could automate them. Now you can with the new fully-automated Bio-Rad DIAMAT™ Analyzer. Among its many advantages are:

Rapid measurement. Less than 8 minutes per test. Provides accurate and precise quantitative data on HbA_{1a}, A_{1b}, A_{1c} and HbF.

Economical. Hands-off operation, minimum reagent use, and rapid performance add up to the lowest cost per test of any method.

Schiff base eliminated. The DIAMAT technique eliminates labile Schiff base interference.

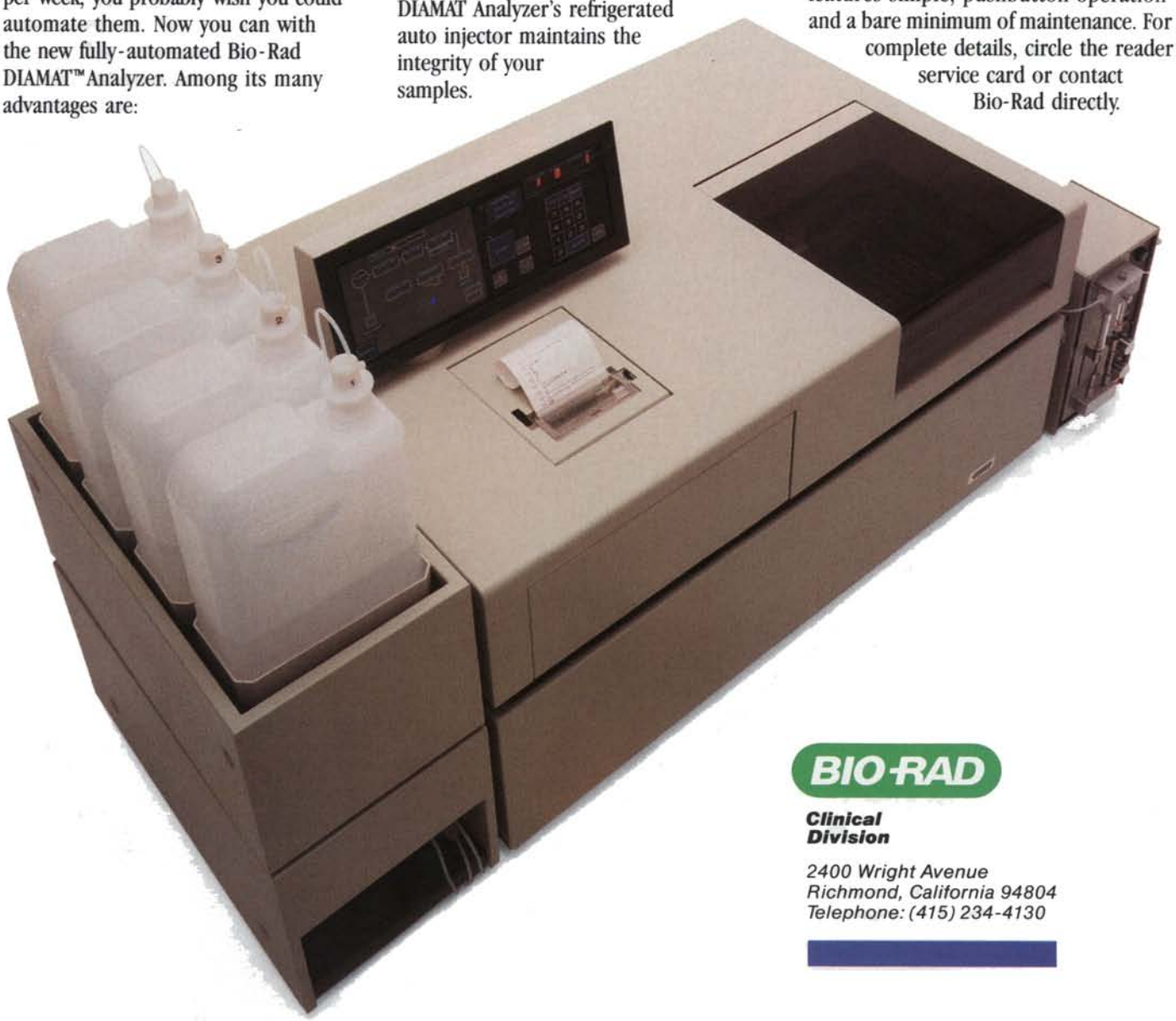
Refrigerated autosampler. The DIAMAT Analyzer's refrigerated auto injector maintains the integrity of your samples.

Up to 48 samples can be handled by this device at one time.

Correlation with column test.

Studies performed in our laboratories show an excellent correlation ($r=0.993$) between DIAMAT Analyzer system values and those obtained from the Bio-Rad Hemoglobin A_{1c} by column test.

More than that, the DIAMAT Analyzer features simple, pushbutton operation and a bare minimum of maintenance. For complete details, circle the reader service card or contact Bio-Rad directly.



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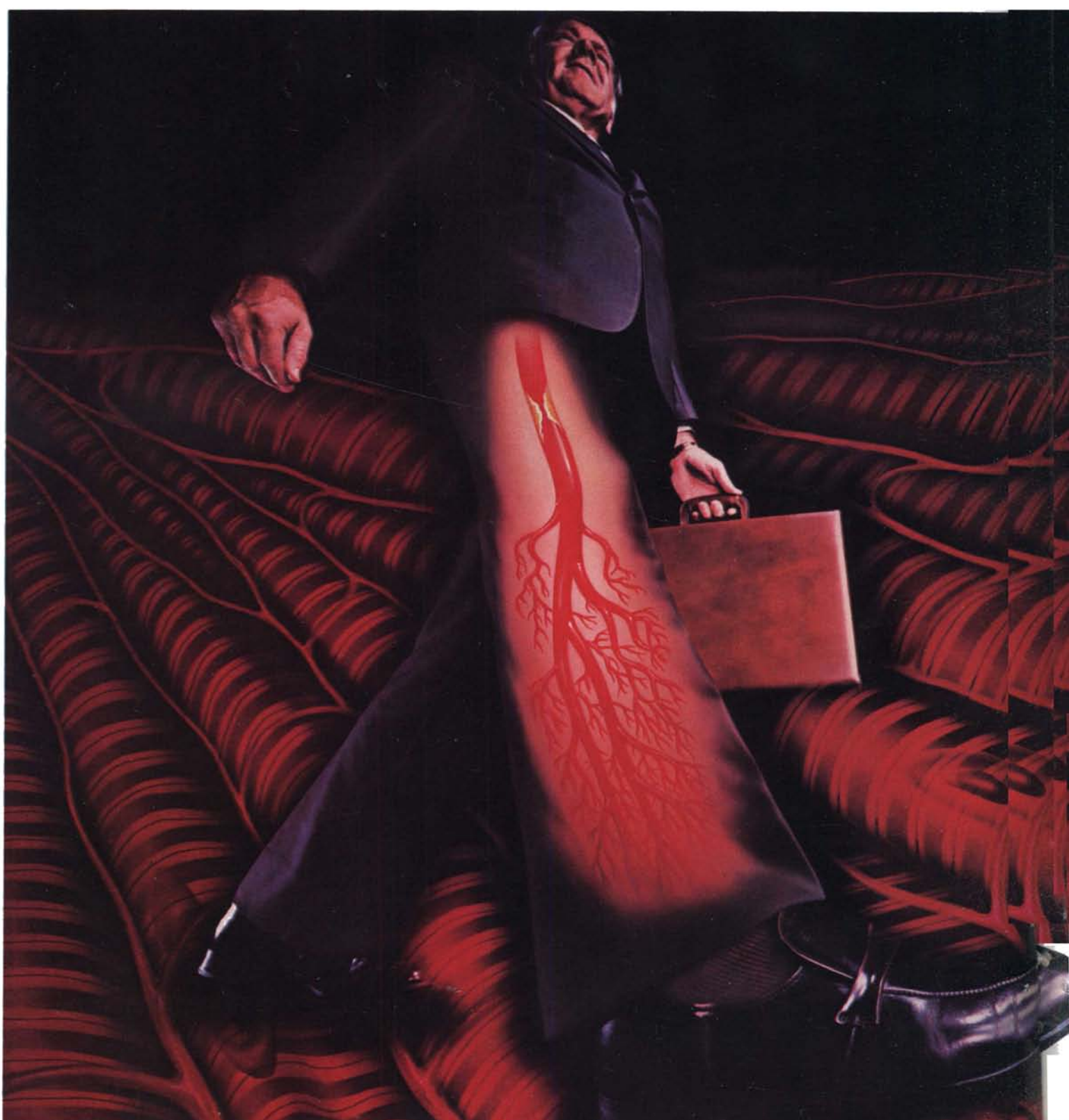
A MILESTONE

The first proven- for intermittent



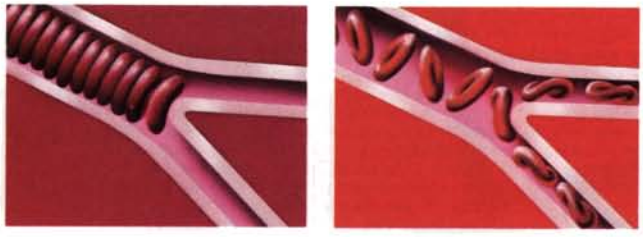
effective agent claudication:

AN IMPORTANT CONTRIBUTION TO THERAPY FROM HOECHST-ROUSSEL

- Not a vasodilator
- Not an anticoagulant
- Not related to aspirin or dipyridamole

Improves microcirculatory blood flow to ischemic tissues

In chronic arterial occlusive disease, the narrowing of an artery high in the leg reduces blood flow to the calf muscles. Elevated blood viscosity, often associated with reduced flow and tissue ischemia, limits flow still further.[1] In addition, another key property affecting microcirculatory blood flow is impaired: the normal capacity of erythrocytes to flex and pass through the capillary lumen, which is narrower than the mean diameter of the erythrocytes. The flow of oxygenated blood to the tissue is limited even more severely, and painful claudication limits the distance patients can walk.

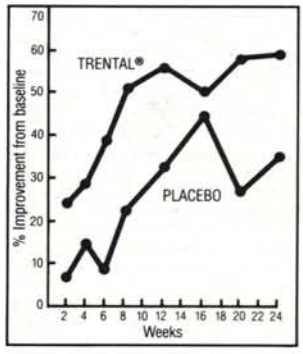


Trental® improves perfusion of ischemic tissue. Current evidence indicates that Trental® helps establish normal blood flow by lowering blood viscosity and by restoring erythrocyte flexibility.[2,3]

Increases pain-free walking distance

Clinical studies have confirmed that patients treated with Trental® can walk significantly farther, and for longer periods of time, than those given placebo.

In a double-blind, multicenter clinical study, Trental®-treated patients showed a 59% mean improvement over baseline by week 24—as compared with 36% improvement shown by patients who received placebo.[4] At baseline the mean walking distances on a treadmill (7° grade) were 111 m for Trental® and 117 m for placebo. 82 evaluated (42 Trental®, 40 placebo).



Well tolerated in long-term therapy

Since 1972, millions of patients in over 50 countries have been treated with Trental®. Side effects are usually mild and transient, generally confined to reversible nausea, dyspepsia, dizziness or headache. No clinically important changes in blood chemistry have been seen. And Trental® is compatible for concurrent use with antihypertensive, beta blocker, digitalis, diuretic, antidiabetic and antiarrhythmic regimens. (See prescribing information.)

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

The usual dosage of Trental® is one 400 mg tablet, taken three times a day with meals. Trental® tablets are packaged in bottles of 100.

While the clinical benefits of Trental® may be seen within 2 to 4 weeks, it is recommended that treatment be continued for at least 8 weeks.

Trental®

400 mg Tablets

(pentoxifylline)

Significantly increases pain-free walking distance.

Please see last page of advertisement for references and a brief summary of prescribing information.

References:
1. Dormandy JA, et al: Clinical, haemodynamic, rheological, and biochemical findings in 126 patients with intermittent claudication. *Br Med J 4:* 576-581, 1973. **2.** Smud R, et al: Changes in blood viscosity induced by pentoxifylline. *Pharmatherapeutica 1*(4):229-233, 1976. **3.** Angelkort B, et al: Influence of pentoxifylline on erythrocyte deformability in peripheral occlusive arterial disease. *Curr Med Res Opin 6*(4):255-258, 1979. **4.** Porter JM, Cutler BS, Lee BY, et al: Pentoxifylline efficacy in the treatment of intermittent claudication: Multicenter controlled double-blind trial with objective assessment of chronic occlusive arterial disease patients. *Am Heart J 104*(2):66-72, July 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: No drug interactions with Trental® (pentoxifylline) are known at this time. Although there have been no formal interaction studies, the drug 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 capsules 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

A giant step toward compliance...

- Medication
- Diet
- Stopping smoking
- Exercise

Ask your Hoechst-Roussel representative for information about this innovative patient education program.

Trental® 400 mg Tablets
(pentoxifylline)

The first proven-effective agent for intermittent claudication

Q7359-585

The most important letters we get at LifeScan look like this.

Dear Lifescan,
Thank you very much for my Glucoscan meter.
I can work it very well now, and I know it is really going to help control my diabetes.

Sincerely yours,
Drew McFadden
(age 7)

To find out how you can obtain your own GLUCOSCAN™ Personal Blood Glucose Monitoring System, call us for the name of your nearest LifeScan Distributor.
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California (800) 982-6132.

Actual unsolicited letter from 7-year-old GLUCOSCAN user, Drew McFadden. Printed by permission of Master McFadden, who even let us take this picture.

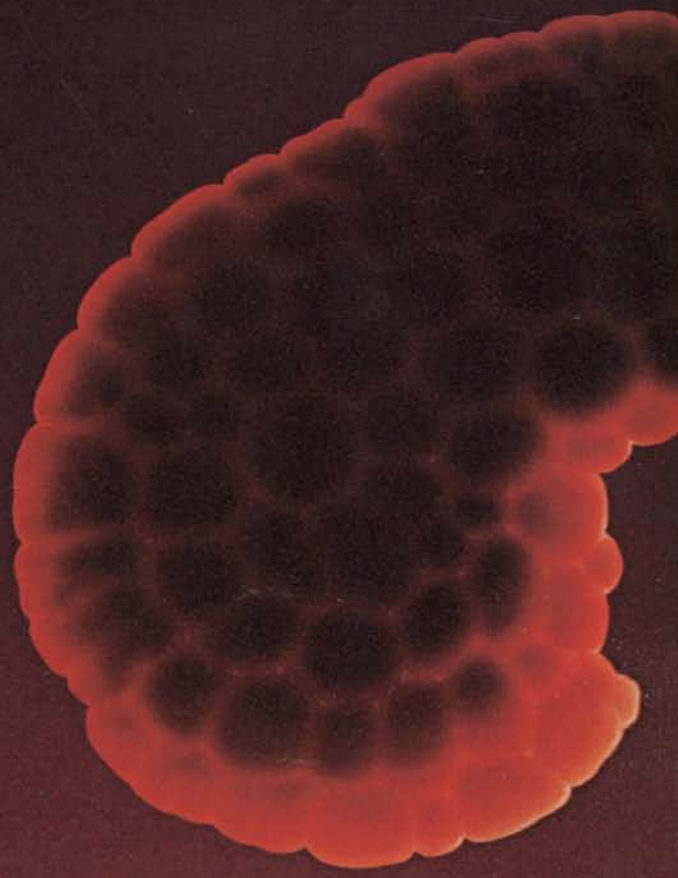
Drew McFadden and his GLUCOSCAN

A Commitment to Personal Diabetes Control–For Life

LIFESCAN INC.
1025 Terra Bella Ave.
Mountain View, CA 94043

Tolinase® Tablets and diet help put the
(tolazamide)

In most type II diabetic patients, insulin levels may be normal or even elevated, but glucose metabolism is less than normal. Tolinase Tablets pharmacologically influence the way the body metabolizes glucose.



The insulin paradox

The coexistence of normal or elevated insulin levels and elevated glucose levels is a common paradox in patients with type II (non-insulin-dependent) diabetes. This condition suggests a lack of tissue sensitivity to endogenous insulin–a phenomenon many investigators today refer to as cellular insulin resistance.

The failure of normal or above-normal amounts of endogenous insulin to produce a normal response in terms of glucose metabolism is believed to result most often from one or more underlying factors, such as beta-cell defects (inadequate or delayed initial response), defects at the cellular receptor and/or postreceptor level, or hepatic defects.

Initial therapy: A rational approach

Since insulin insufficiency is probably not the basic problem in type II diabetes, diet and exercise are considered the cornerstones of therapy because they help correct the cause of the underutilization of insulin (eg, receptor defect) and may help lower blood glucose. If diet and regular exercise fail to control glucose levels adequately, **Tolinase** Tablets are an appropriate addition to the regimen.

How Tolinase Tablets influence glucose metabolism

The primary mode of action of **Tolinase** Tablets is to lower serum glucose in responsive patients by stimulating the release of additional insulin **(1)**. As therapy continues, it is believed that **Tolinase** promotes peripheral glucose metabolism by helping to correct defects at the cellular receptor **(2)** and postreceptor **(3)** level. In this environment, tissue sensitivity and responsiveness to insulin increase, glucose levels decrease, and insulin levels frequently return toward normal.

Once-a-day dosage with Tolinase Tablets

has been shown to be just as effective as a divided dose in the treatment of non-insulin-dependent diabetes.

Although the interpretations are controversial, the UGDP study reported in 1970 that the use of tolbutamide, an oral hypoglycemia drug, was associated with increased cardiovascular mortality.

As with all sulfonylureas, hypoglycemia may occur. No sulfonylurea should be given to patients with serious kidney, liver, or endocrine disease. **Tolinase** is not indicated in patients with a history of repeated ketoacidosis or coma.

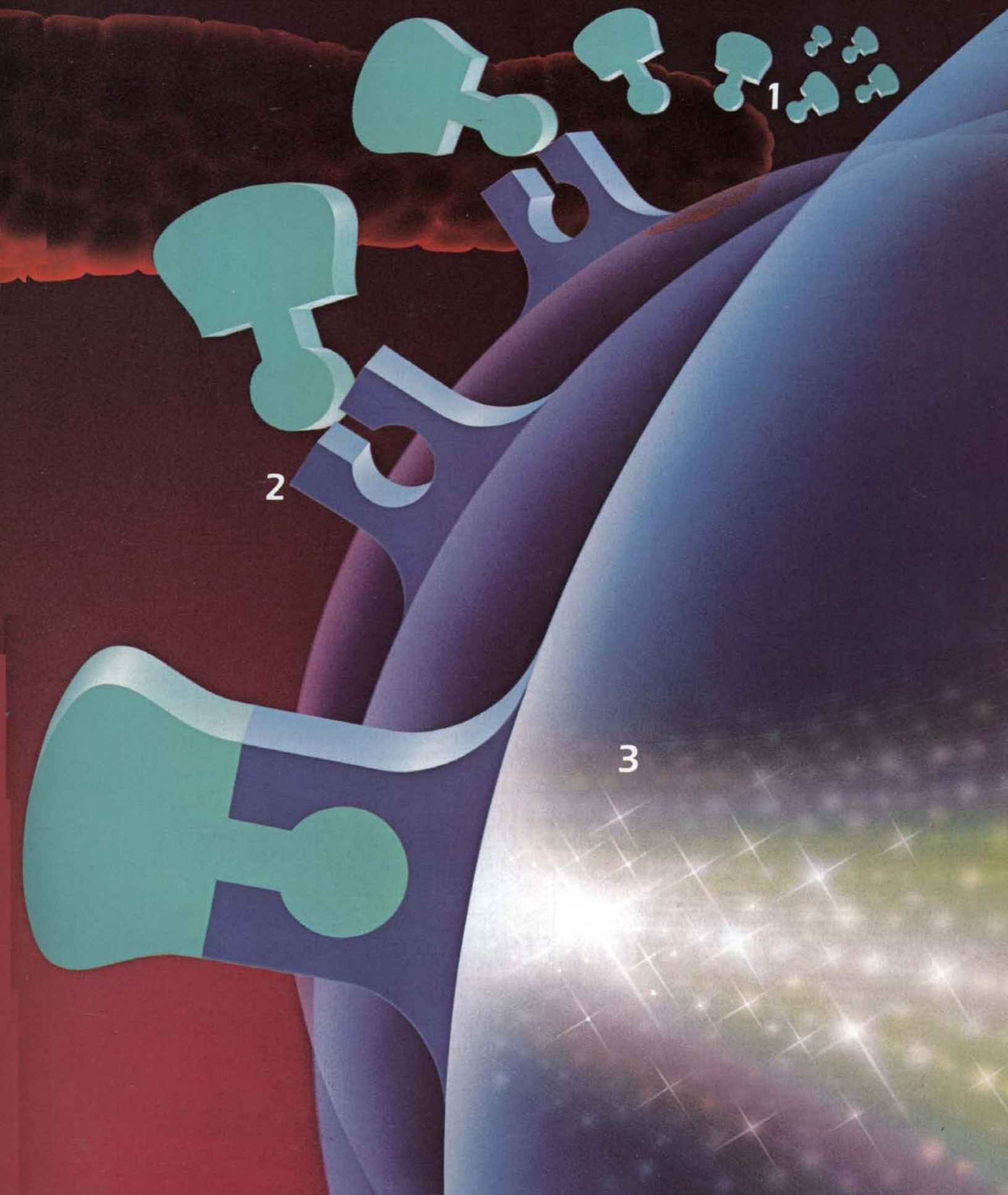
Tolinase® 100, 250 & 500 mg tablets
(tolazamide)

Once a day

For a brief summary of prescribing information, please turn the pag

Upjohn
The Upjohn Company
Kalamazoo, Michigan 49001

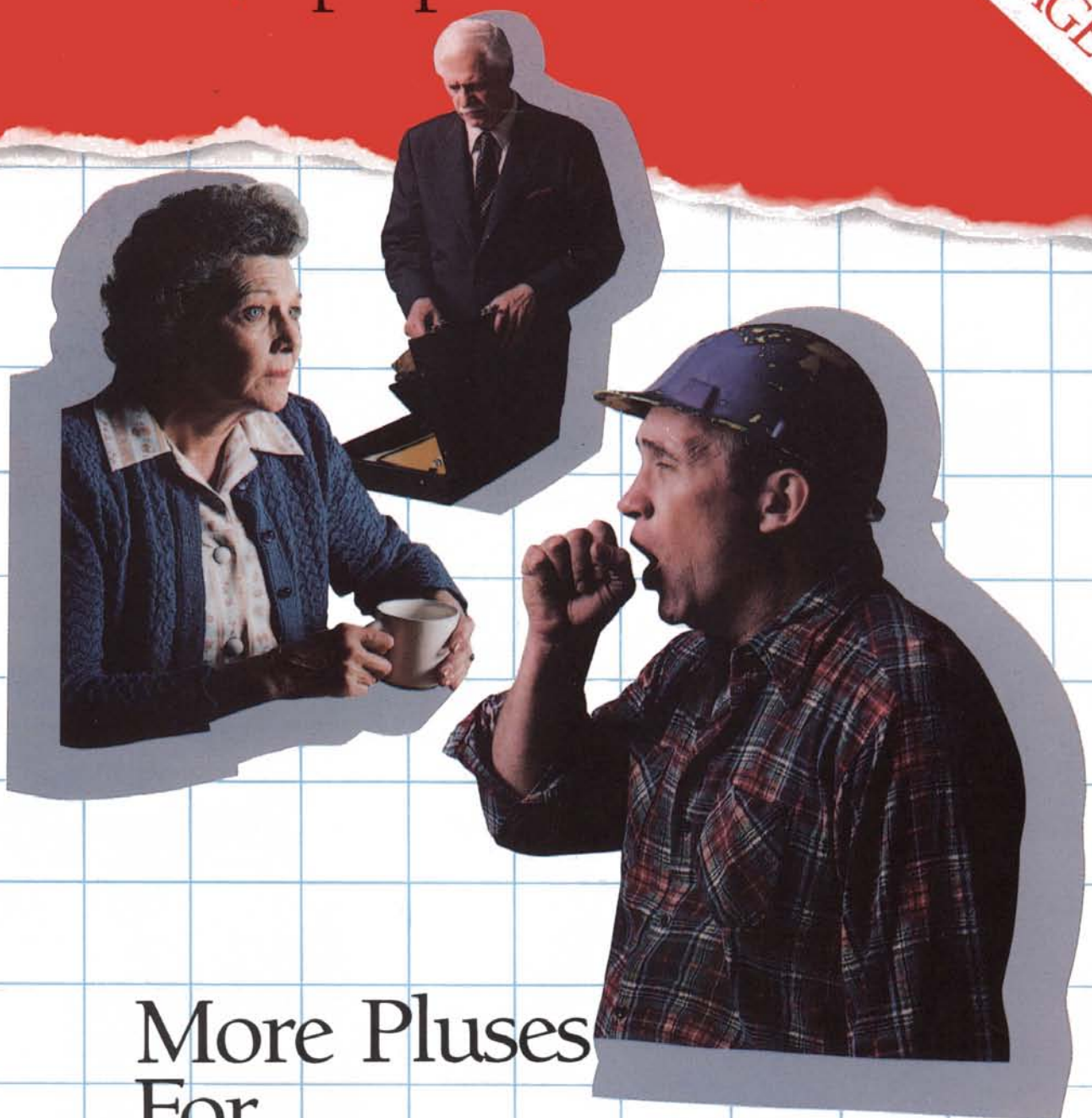
patient's own insulin back to work.



NEW–BID DOSAGE

ACE* INHIBITOR

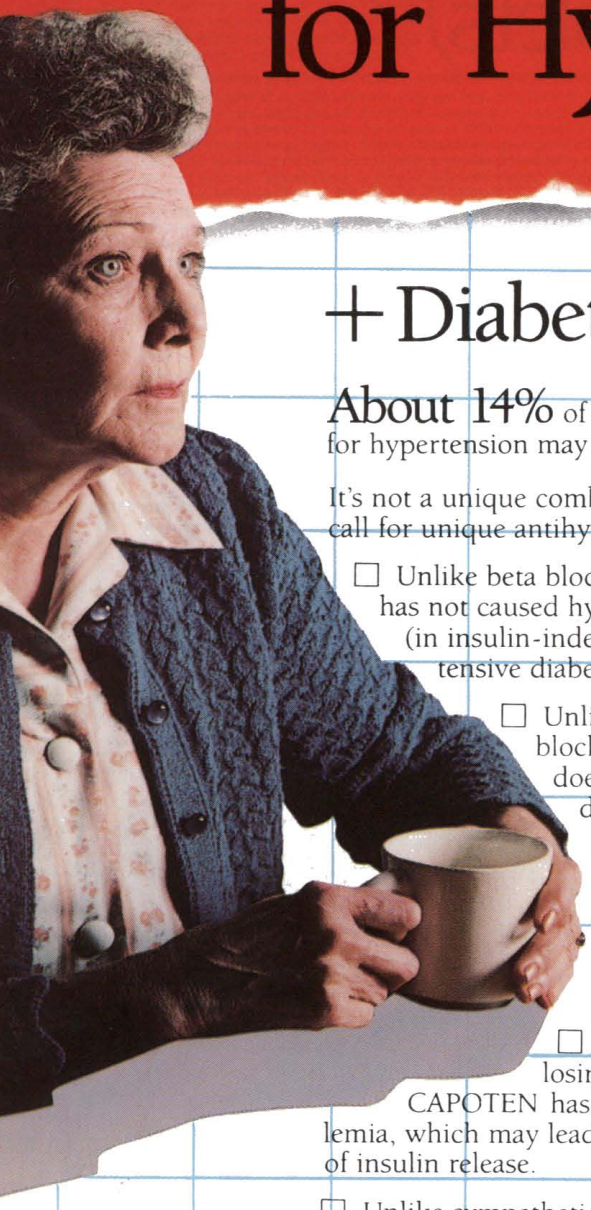
Capoten®
(captopril tablets)



More Pluses For Hypertension-Plus Patients

*Angiotensin Converting Enzyme

Capoten® (captopril tablets) for Hypertension†-Plus...



+ Diabetes†

About 14% of patients treated for hypertension may also have diabetes.[1]

It's not a unique combination. But it can call for unique antihypertensive therapy.

☐ Unlike beta blockers,[2,3] CAPOTEN has not caused hyperglycemia (in insulin-independent hypertensive diabetics).

☐ Unlike some beta blockers,[2,3] CAPOTEN does not mask the dizziness and sweating often occurring with hypoglycemia (in insulin-dependent hypertensive diabetics).

☐ Unlike potassium-losing diuretics,[2,3] CAPOTEN has not caused hypokalemia, which may lead to suppression of insulin release.

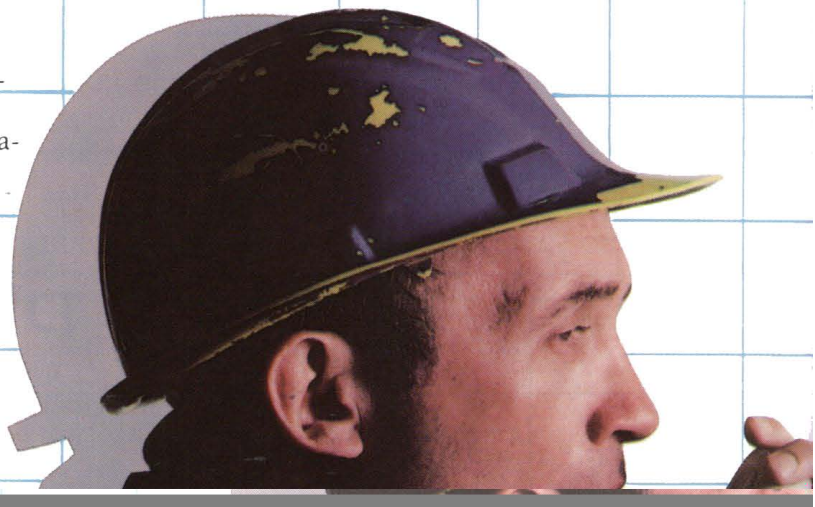
☐ Unlike sympathetic inhibitors,[3] CAPOTEN rarely affects sexual potency (which may already be compromised in diabetic men).

+ Bronchospastic pulmonary disease†

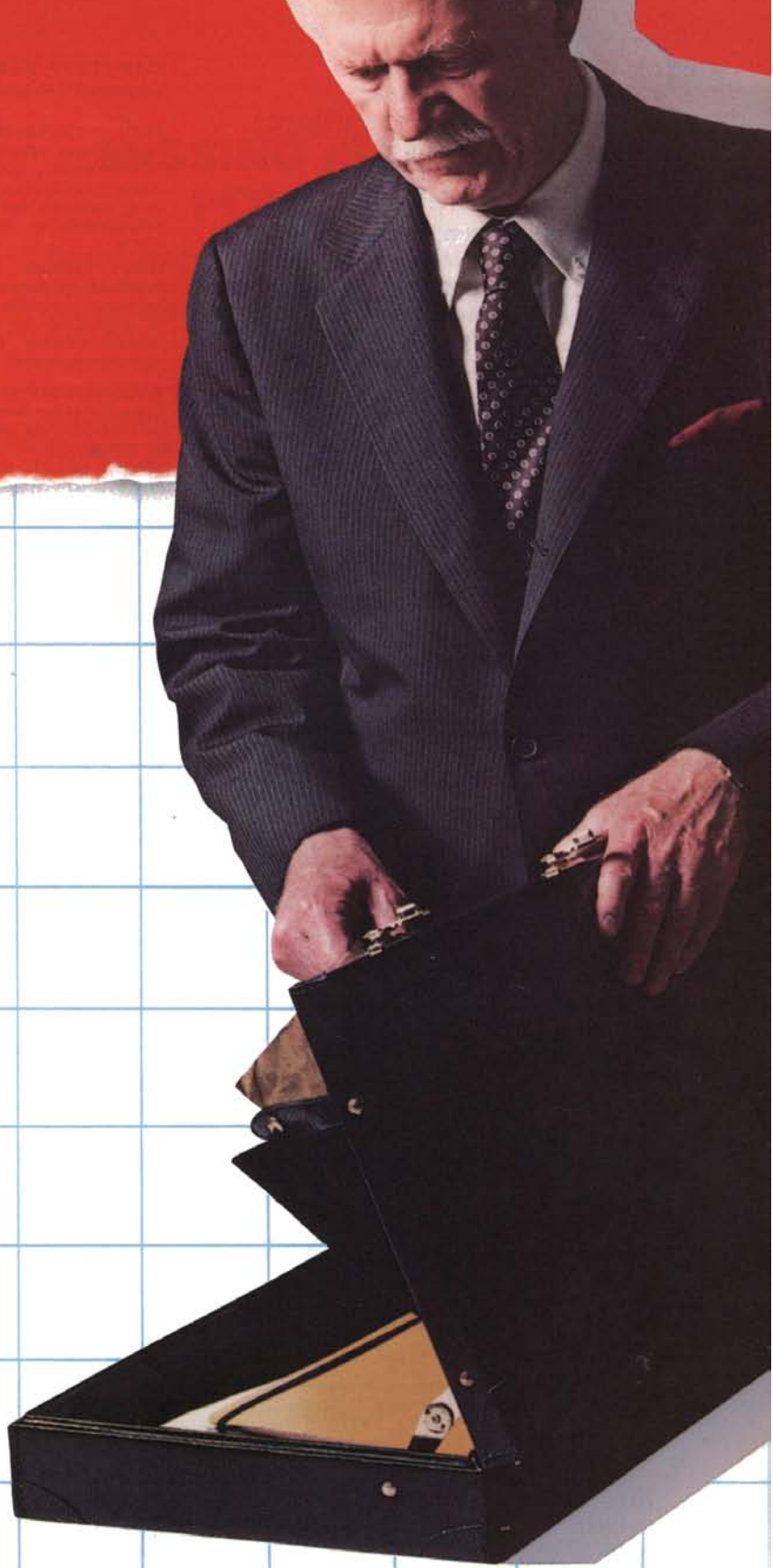
About 7% of patients treated for hypertension may also have asthma.[1]

A problem that may call for an uncommon antihypertensive solution.

☐ CAPOTEN rarely causes bronchospasm.[4]



Please see Precautionary Guidelines for use of CAPOTEN and brief summary of prescribing information, especially the INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS [illegible]



+ Heart failure†

Approximately 13%

of patients treated for hypertension may also have heart failure.[1]

Moreover, the Framingham study demonstrated that 75% of patients with heart failure previously had been hypertensive.[1,5] The two disorders may share a common link. They do share a common therapy.

☐ Unlike beta blockers, CAPOTEN lowers blood pressure without the associated decrease in heart rate and cardiac output.

☐ Unlike any other antihypertensive agent, CAPOTEN blocks activation of the renin-angiotensin-aldosterone (RAA) system, which may play a role in both heart failure and hypertension.

†CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or have developed unacceptable side effects.
‡Systolic ≥ 160 mm Hg and diastolic ≥ 95 mm Hg in two readings.

ACE* INHIBITOR

Capoten®
(captopril tablets)

The Unique Solution for the Hypertension-Plus Patient

*Angiotensin Converting Enzyme

ACE* INHIBITOR

Capoten®
(captopril tablets)

Precautionary Guidelines

CAPOTEN has been associated with the development of neutropenia/agranulocytosis (0.3% of 4,000 patients) or proteinuria (1.2% of 4,000 patients).† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the autoimmune response.

The following precautionary guidelines are recommended for all patients receiving CAPOTEN:

☐ **Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.**

☐ **Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.**

☐ **Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.**

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

*Angiotensin Converting Enzyme

†Please see the following brief summary of prescribing information for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

References:
1. Market Measures Inc.: Treatment of Hypertension V, February 1983.
2. Christlieb AR: Management of hypertension in the patient with diabetes mellitus. Practical Cardiol 8:94-103, 1982.
3. Christlieb AR: Diabetes and hypertension. Cardiovasc Rev Reports 1:609-616, 1980.
4. Data on file, Squibb Institute for Medical Research.
5. McKee PA, Castelli WP, McNamara PM, et al: The natural history of heart failure: The Framingham study. N Engl J Med 285:1441-1446, 1971.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension—Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.

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: Proteinuria—Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. 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.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine—the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis—Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. 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.

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 blood pressure >20% were recorded in about ½ 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.

PRECAUTION: 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 3 hours 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. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.

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.

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.

Usage in Pregnancy: 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.

(Continued on next page)

(Continued from preceding page)

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 about 4000 patients.

Renal—One to 2 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 occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic—Rash (usually mild, maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, 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 100 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 in about 2 of 100 patients. See WARNINGS (Hypotension) 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 7 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, 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 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 in 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 should be taken one hour before meals. 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 25, 50, and 100 mg in bottles of 100, and in UNIMATIC® unit-dose packs of 100 tablets.

Princeton, NJ 08540 525-552
Issued: January 1985

SQUIBB

Pfizer is talking to people about diabetes.

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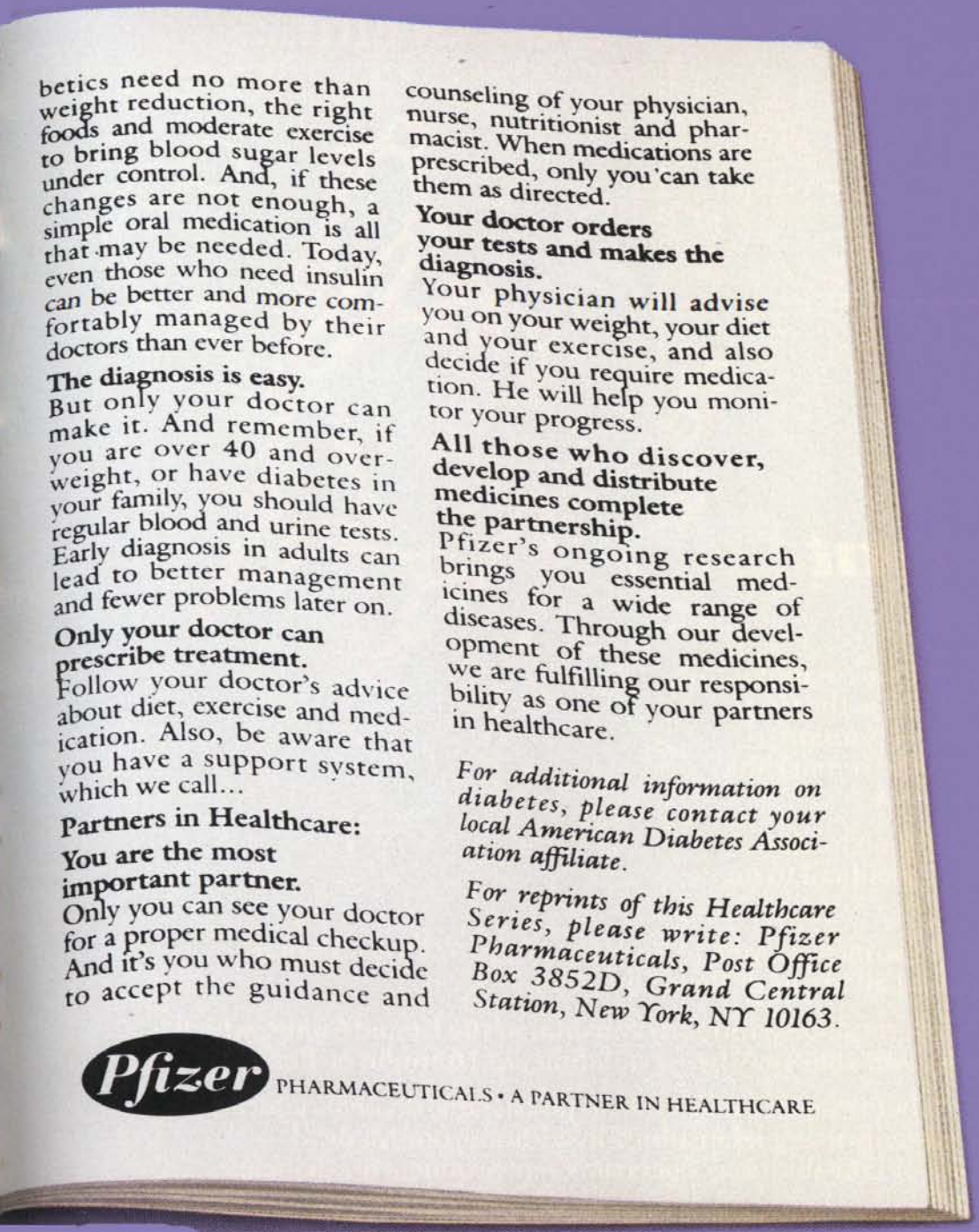
so that they will talk to their doctors.



betics need no more than weight reduction, the right foods and moderate exercise to bring blood sugar levels under control. And, if these changes are not enough, a simple oral medication is all that may be needed. Today, even those who need insulin can be better and more comfortably managed by their doctors than ever before.

The diagnosis is easy.
But only your doctor can make it. And remember, if you are over 40 and overweight, or have diabetes in your family, you should have regular blood and urine tests. Early diagnosis in adults can lead to better management and fewer problems later on.

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You are the most important partner.
Only you can see your doctor for a proper medical checkup. And it's you who must decide to accept the guidance and counseling of your physician, nurse, nutritionist and pharmacist. When medications are prescribed, only you can take them as directed.

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Your physician will advise you on your weight, your diet and your exercise, and also decide if you require medication. He will help you monitor your progress.

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Pfizer's ongoing research brings you essential medicines for a wide range of diseases. Through our development of these medicines, we are fulfilling our responsibility as one of your partners in healthcare.

For additional information on diabetes, please contact your local American Diabetes Association affiliate.

For reprints of this Healthcare Series, please write: Pfizer Pharmaceuticals, Post Office Box 3852D, Grand Central Station, New York, NY 10163.

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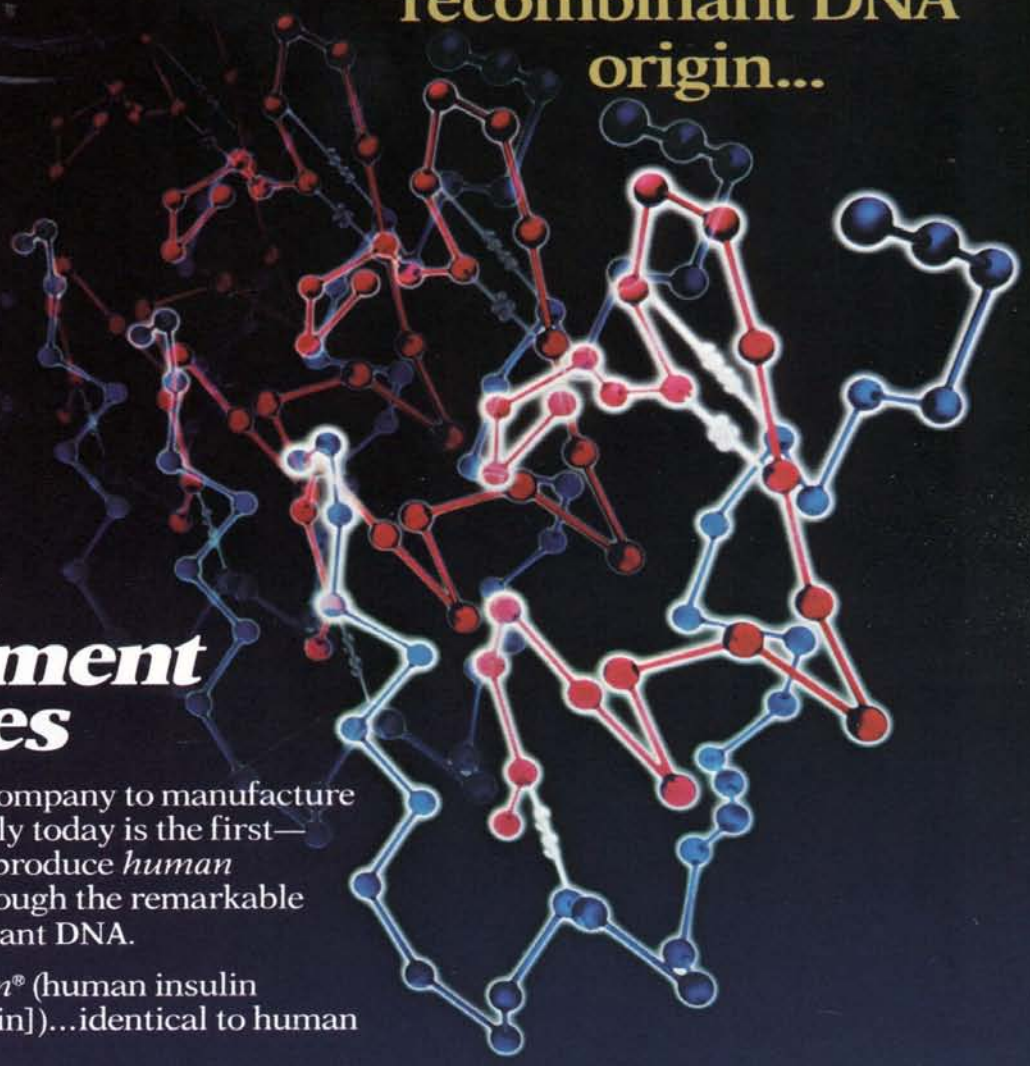

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