SEPTEMBER 1985 VOLUME 34 NUMBER 9

diabetes

A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION.

ORIGINAL CONTRIBUTIONS

RAPID PUBLICATIONS

DIAEAZ 34(9) 831–949 (1985)
ISSN 0012-1797

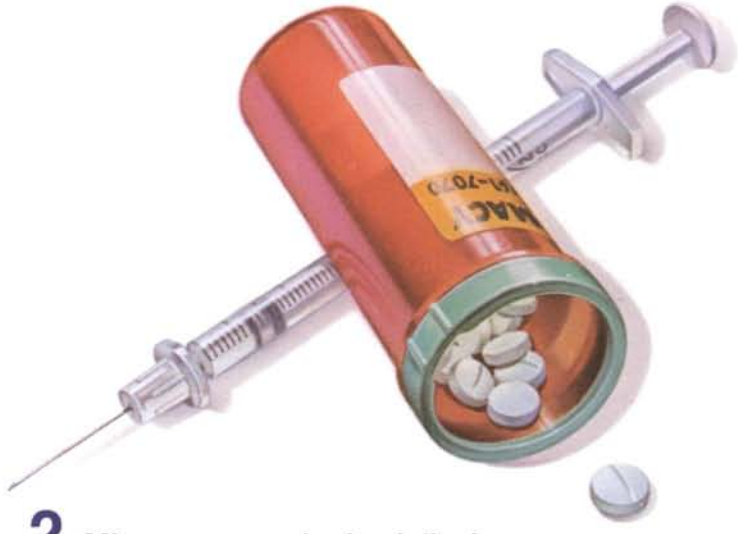
When a type II diabetic patient needs more than diet, unique MICRONASE® Tablets (glyburide) are a logical first choice.

Choosing antidiabetic

1. Micronase—a rational choice in type II diabetes

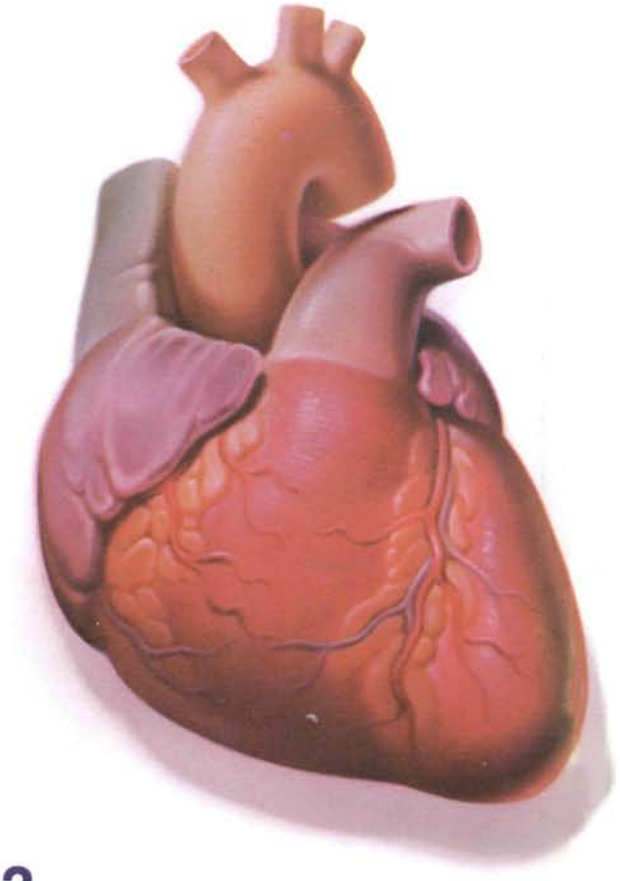
Insulin levels are normal or elevated in most patients with type II diabetes, although insulin action is markedly impaired. MICRONASE helps normalize the tissue response to endogenous insulin.

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.



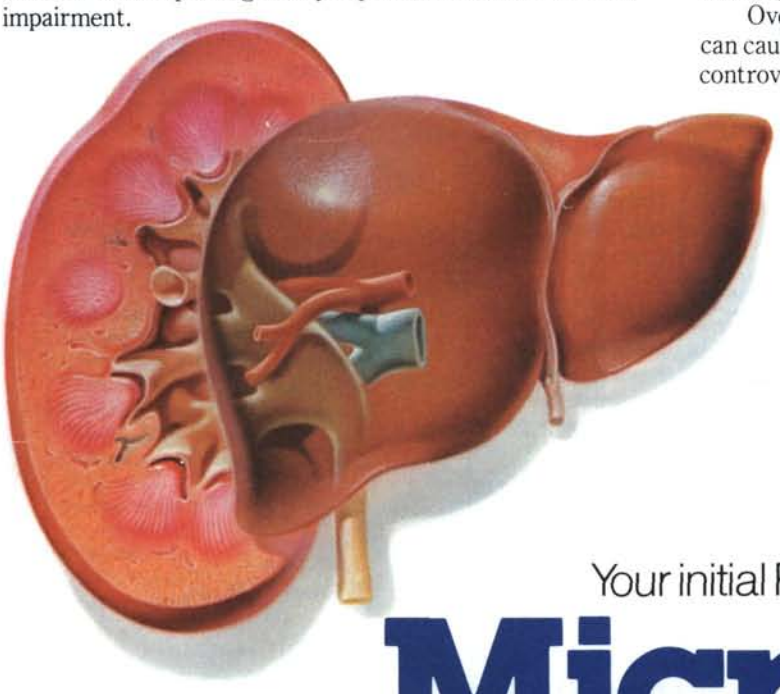
3. Micronase—for the type II diabetic patient who is also hypertensive: Control without risk of water retention

This may also be significant for the type II diabetic patient with congestive heart failure. MICRONASE actually causes a 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.

SEPTEMBER AUTHOR INDEX

(Volume 34, Number 9)

diabetes
A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION®

DIABETES is published by the American Diabetes Association, Inc., to provide an official Journal for the Association and to furnish the medical profession with information concerning diabetes and related fields of medicine.

The Journal does not publish material that has been reported elsewhere. In submitting an article the author(s) must state in the covering letter that the material has not been published elsewhere and has not been submitted for publication elsewhere. Prior publication specifically includes symposia, proceedings, preliminary communications, books, and invited articles. It is assumed that all human investigation shall have been conducted according to the principles expressed in the Declaration of Helsinki. Accepted manuscripts incur a charge of $25 per printed page.

For studies involving experimental animals, state the species, strain, number used, and other pertinent descriptive characteristics. For human subjects or patients, describe their characteristics. When describing surgical procedures on animals, identify the preanesthetic and anesthetic agents used, and state the amount or concentration and the route and frequency of administration for each. The use of paralytic agents, such as curare or succinylcholine, is not an acceptable substitute for anesthetics. For other invasive procedures on animals, report the analgesic or tranquilizing drugs used; if none was used, provide justification for such exclusion. When reporting studies on unanesthetized animals or on humans, indicate that the procedures followed were in accordance with institutional guidelines.

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All signed articles and editorials are the responsibility of the author(s) and not that of the American Diabetes Association. The Editors will be pleased to consider for publication papers presented at the Annual Meeting of the Association.

Rapid Publications: Observations considered to be of unusual importance may be submitted as a Rapid Publication. Editorial decision will be made within 10 days after receipt of the manuscript. No written review or explanation of the decision will be provided. Rejected papers may be resubmitted as a regular manuscript and reviewed accordingly. Rapid Publications may not exceed 10 double-spaced typewritten pages (including figures, tables, and references). Accepted papers will be published in the earliest possible issue of the Journal.

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.

An abstract or summary of the content of the paper of not more than 250 words should be provided. This should be self-contained and understandable without reference to the text.

Photographs, drawings, and figures should be suitable for reproduction. Photographs should be unmounted, untrimmed glossy prints. The names of authors should appear on the back. The tops of photographs and figures should be indicated.

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All manuscripts and related correspondence should be addressed to Charles J. Goodner, M.D., Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. Editorial correspondence should be addressed to the Editorial Office, DIABETES, American Diabetes Association, Inc., 2 Park Avenue, New York, New York 10016.

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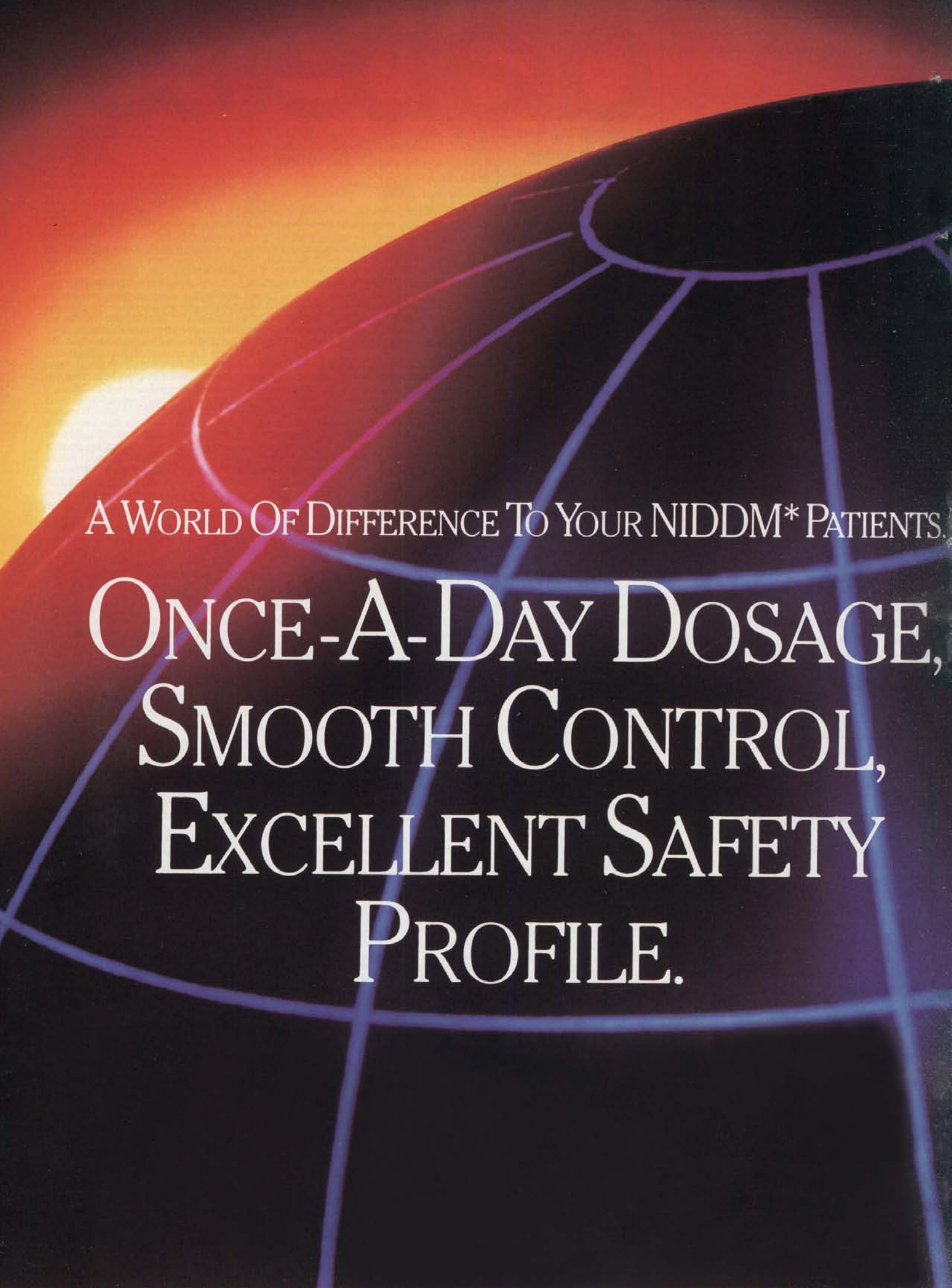
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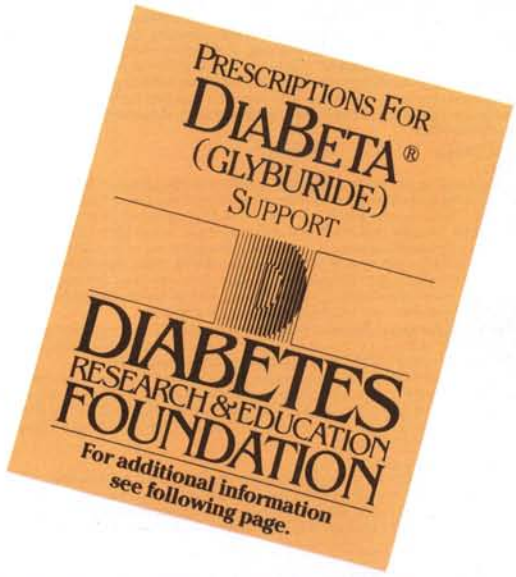
*Non-Insulin-Dependent Diabetes Mellitus

†Caution, of course, should be exercised in patients with renal or hepatic impairment. Hepatic insufficiency may diminish gluconeogenesis and also may cause elevated blood levels of DiaBeta; both of which increase the risk of serious hypoglycemic reactions.



As an adjunct to diet and exercise

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Hoechst

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Please see next page for brief summary of Prescribing Information.

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DiaBeta® (glyburide) Tablets 1.25, 2.5 and 5 mg

BRIEF SUMMARY

INDICATIONS AND USAGE

DiaBeta® (glyburide) is indicated as an adjunct to diet to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (Type II) whose hyperglycemia cannot be controlled by diet alone.

In initiating treatment for non-insulin-dependent diabetes, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered. Use of DiaBeta® (glyburide) must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone may be transient, thus requiring only short-term administration of DiaBeta® (glyburide).

During maintenance programs, DiaBeta® (glyburide) should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations.

In considering the use of DiaBeta® (glyburide) in asymptomatic patients, it should be recognized that controlling the blood glucose in non-insulin-dependent diabetes has not been definitely established to be effective in preventing the long-term cardiovascular or neural complications of diabetes.

CONTRAINDICATIONS

DiaBeta® (glyburide) 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 DiaBeta® (glyburide) 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 DiaBeta® (glyburide) 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.

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 DiaBeta® (glyburide) and administer insulin.

The effectiveness of any oral hypoglycemic drug, including DiaBeta® (glyburide), 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.

Information for patients

Patients should be informed of the potential risks, advantages, alternative modes of therapy, importance of adherence to dietary instructions, to a regular exercise program, and regular testing of urine and/or blood glucose. Also explain to the patient and responsible family members, the risks of hypoglycemia, its symptoms, treatment, conditions that predispose to its development, and primary and secondary failure.

Laboratory Tests

Blood and urine glucose should be monitored periodically. Measurement of glycosylated hemoglobin may be useful.

Drug Interactions

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. When such drugs are administered to a patient receiving DiaBeta® (glyburide), the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving DiaBeta® (glyburide), the patient should be observed closely for loss of control.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving DiaBeta® (glyburide), the patient should be closely observed for loss of control. When such drugs are withdrawn from a patient receiving DiaBeta® (glyburide), the patient should be observed closely for hypoglycemia.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

DiaBeta® (glyburide) is non-mutagenic when studied in the Salmonella microsome test (Ames test) and in the DNA damage/alkaline elution assay. Studies in rats at doses up to 300 mg/kg/day for 18 months showed no carcinogenic effects.

Pregnancy

Teratogenic Effects: Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 500 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to DiaBeta® (glyburide). There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects:

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. If DiaBeta® (glyburide) is used during pregnancy, it should be discontinued at least two weeks before the expected delivery date.

Nursing Mothers

Although it is not known whether DiaBeta® (glyburide) is excreted in human milk, some sulfonylureas are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue administering the drug, taking into account the importance of the drug to the mother. If DiaBeta® (glyburide) is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Hypoglycemia: See **PRECAUTIONS** and **OVERDOSAGE** Sections.

Gastrointestinal Reactions: Cholestatic jaundice may occur rarely; DiaBeta® (glyburide) should be discontinued if this occurs. Gastrointestinal disturbances, e.g., nausea, epigastric fullness, and heartburn, are the most common reactions and occur in 1.8% of treated patients. They tend to be dose-related and may disappear when dosage is reduced.

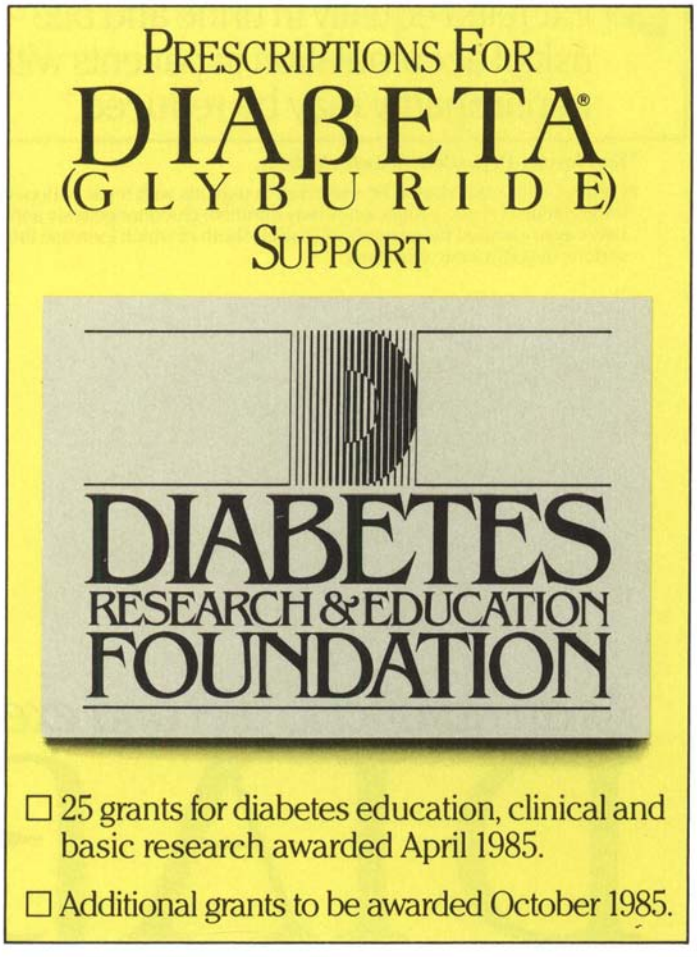
Dermatologic Reactions: Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in 1.5% of treated patients. These may be transient and may disappear despite continued use of DiaBeta® (glyburide); if skin reactions persist, the drug should be discontinued.

Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

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

Metabolic Reactions: Hepatic porphyria reactions have been reported with sulfonylureas; however, these have not been reported with DiaBeta® (glyburide). Disulfiram-like reactions have been reported very rarely with DiaBeta® (glyburide).

OVERDOSAGE: Overdosage can produce hypoglycemia. Aggressively treat the mild symptoms (without loss of consciousness or neurologic findings) with oral glucose and adjustments in drug dosage and/or meal patterns. Continue close monitoring until patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment, are medical emergencies requiring immediate hospitalization. With hypoglycemic coma (diagnosed or suspected), administer rapid intravenous injection of concentrated (50%) glucose solution, followed by continuous infusion of a more dilute (10%) glucose solution at a rate to maintain a blood glucose level above 100 mg/dL. Monitor closely for a minimum of 24-48 hours; hypoglycemia may recur after apparent clinical recovery.



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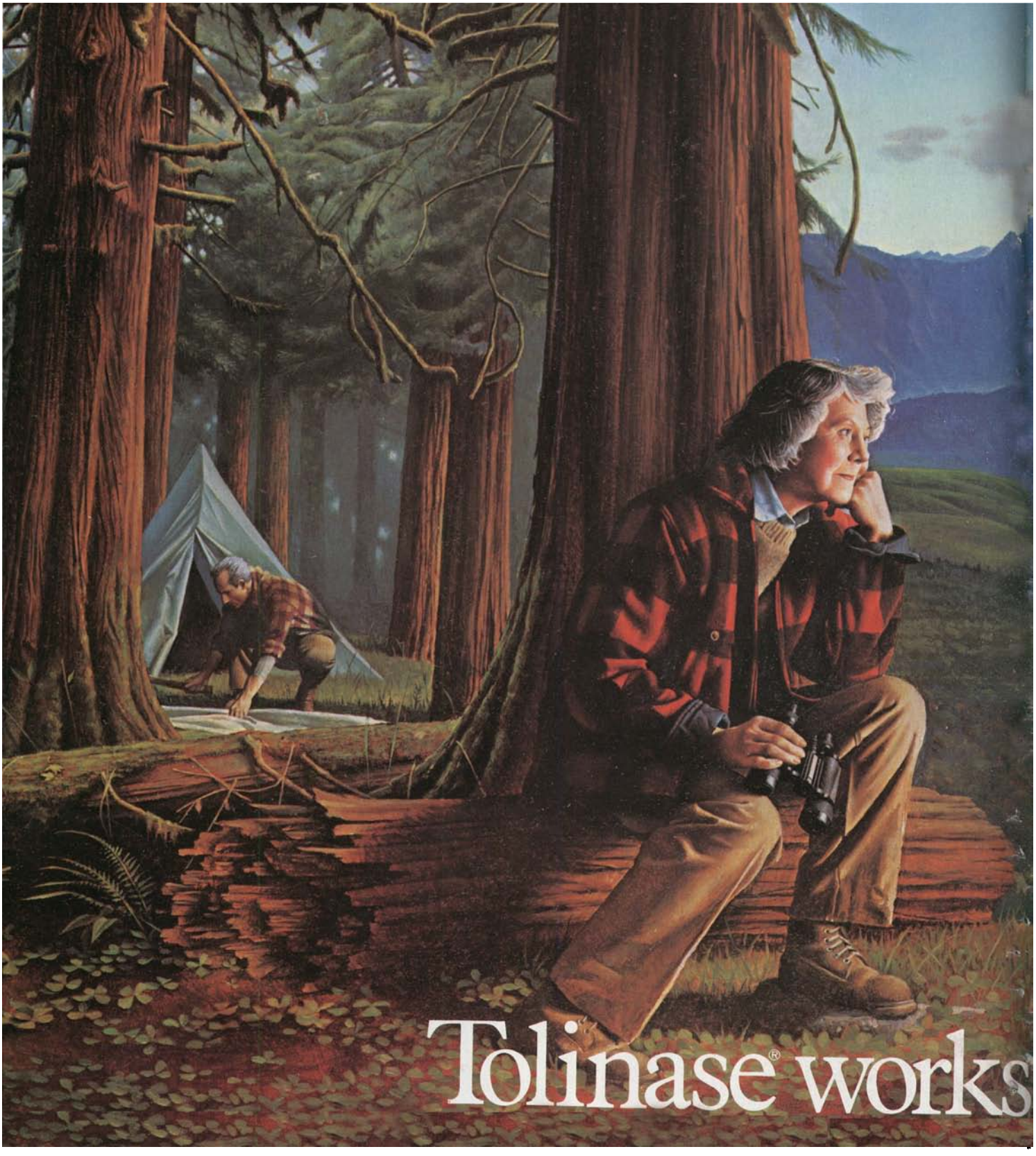

Each once-a-day dose of *Tolinase* is effective for about 24 hours once steady state has been achieved— an important consideration in the management of type II diabetic patients. Most of the urinary excretion occurs within the first 24 hours after administration.

When diet and exercise fail to control glucose levels adequately in type II (non-insulin-dependent) diabetes, TOLINASE Tablets (tolazamide) are a sound addition to the regimen—not only because they provide effective, once-a-day therapy, but also because the action of each dose lasts about

24 hours. Proper patient selection, dosage, and instructions are important in order to avoid hypoglycemic episodes.

Tolinase **causes a mild diuresis—**
an added advantage in patients whose condition may be aggravated by fluid retention (patients with hypertension or congestive heart failure, for example).

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.

In type II diabetes

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

One tablet...one day's therapy

Please turn page for brief summary of prescribing information.

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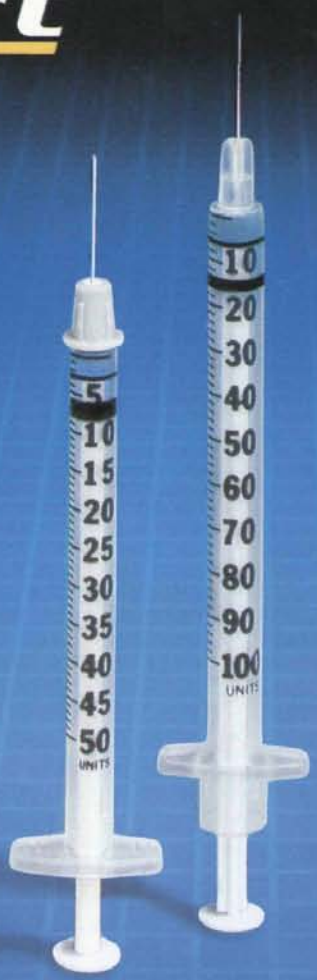

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B-D Better Diabetes Care

Announces

25 Additional Grants Toward A Better Understanding Of Diabetes

The Trustees of the Foundation are pleased to announce the funding of 25 more special projects. Nine grants have been awarded in basic research, eight in clinical research, and eight in education.

Basic Research Grants:

George Liang King, M.D.
Joslin Diabetes Center,
Boston, MA.
"Comparative Analysis of Vascular Cells from Capillaries and Large Arteries from Diabetic and Non-Diabetic Humans and BB/W Rats."

Roger H. Unger, M.D.
University of Texas Southwestern Medical School, Dallas, TX.
"The Role of Hyperglycemia in Beta Cell Damage."

Joseph R. Williamson, M.D.
Washington University School of Medicine, St. Louis, MO.
"Diabetes-Induced Leukocyte Dysfunction: Is It Also an Aldose Reductase-Linked Phenomenon?"

Douglas L. Coleman, Ph.D.
The Jackson Laboratory,
Bar Harbor, ME.
"Etiocholanolones: New Oral Anti-Diabetes and Anti-Obesity Agents."

Gegham Barseghian, M.D.
City of Hope National Medical Center, Duarte, CA.
"Potentiation of Insulin Activity by Ethanolamine."

Stephen Brendan Richardson, M.D.
Department of Medicine, New York University School of Medicine,
New York, NY.
"Insulin Secretion from RINm Cells: A Possible Model for Non-Insulin-Dependent Diabetes Mellitus (NIDDM)."

Robert C. McEvoy, M.D.
Mount Sinai School of Medicine,
New York, NY.
"Development of Cell Lives of Mouse and Human Pancreatic Beta Cells."

Madhur K. Sinha, Ph.D.
East Carolina University School of Medicine, Greenville, NC.
"Demonstration of Insulin Mediator in Serum and Urine: Its Significance in NIDDM."

Carl Grunfeld, M.D., Ph.D.
Department of Medicine, University of California, San Francisco, CA.
"Structure and Function Analysis of the Insulin Receptor Using Antibodies Against Sequence Specific Peptides."

Clinical Research Grants:

Neil B. Ruderman, M.D.
Boston University School of Medicine, Boston, MA.
"Exercise, Thermogenesis and Control of Body Weight."

Donald C. Simonson, M.D.
Yale University School of Medicine,
New Haven, CT.
"Glucose Resistance in Diabetes."

Lalith K. Misra, Ph.D.
Baylor College of Medicine,
Houston, TX.
"Diabetic Neuropathy: A Nuclear Magnetic Resonance Study."

Elliot J. Rayfield, M.D.
Mount Sinai School of Medicine,
New York, NY.
"The Effect of Serum Glucose on Neutrophil Function in Diabetic Patients."

Harvey Jon Kliman, M.D., Ph.D.
Hospital of the University of Pennsylvania, Philadelphia, PA.
"Differentiation and Growth of the Human Trophoblast: The Effects of Insulin and Insulin-like Growth Factors."

Ronald B. Goldberg, M.D.
University of Miami School of Medicine, Miami, FL.
"Remnant Lipoproteins in Type I and II Diabetes Mellitus: Influence of Good Glycemic Control."

Alain D. Baron, M.D.
University of California,
San Diego, CA.
"In Vivo Regulation of Non-insulin Mediated Glucose Uptake in Man."

Richard C. Spielman, Ph.D.
University of Pennsylvania School of Medicine, Philadelphia, PA.
"Family Studies of the Insulin Gene Polymorphin in Type I and II Diabetes."

Education Grants:

Adrienne B. Butler, M.D.
Southeast Health Unit, Waycross, GA.
"Project Retreat: Recreation, Training and Eating Outdoors for Youth With Diabetes."

O. Charles Olson, M.D.
Deaconess Medical Center,
Spokane, WA.
"Is Diabetes Education Effective in Improving the Prognosis for Diabetic Patients?"

Ellie Strock, R.N.
International Diabetes Center,
Minneapolis, MN.
"Diabetes Home Care Program."

Richard R. Rubin, Ph.D.
Johns Hopkins Diabetes Center,
Baltimore, MD.
"Evaluation of an Intensive Diabetes Education Program Incorporating Coping Skills Training."

Marla Bernbaum, M.D.
St. Louis University School of Medicine, St. Louis, MO.
"A Clinical Program for the Visually Impaired Diabetic Patient."

Maria Luisa Urdaneta, R.N., Ph.D.
Social Science Research Administration, San Antonio, TX.
"The Impact of Sociocultural Factors on Compliance to Treatment Regimens Among Mexican American Diabetics."

Jeanne B. Groner, M.S.W.
New York College of Podiatric Medicine, New York, NY.
"Comprehensive Diabetic Information Program."

Linda F. Samson, M.N., R.N.C.
University of Pennsylvania,
Philadelphia, PA.
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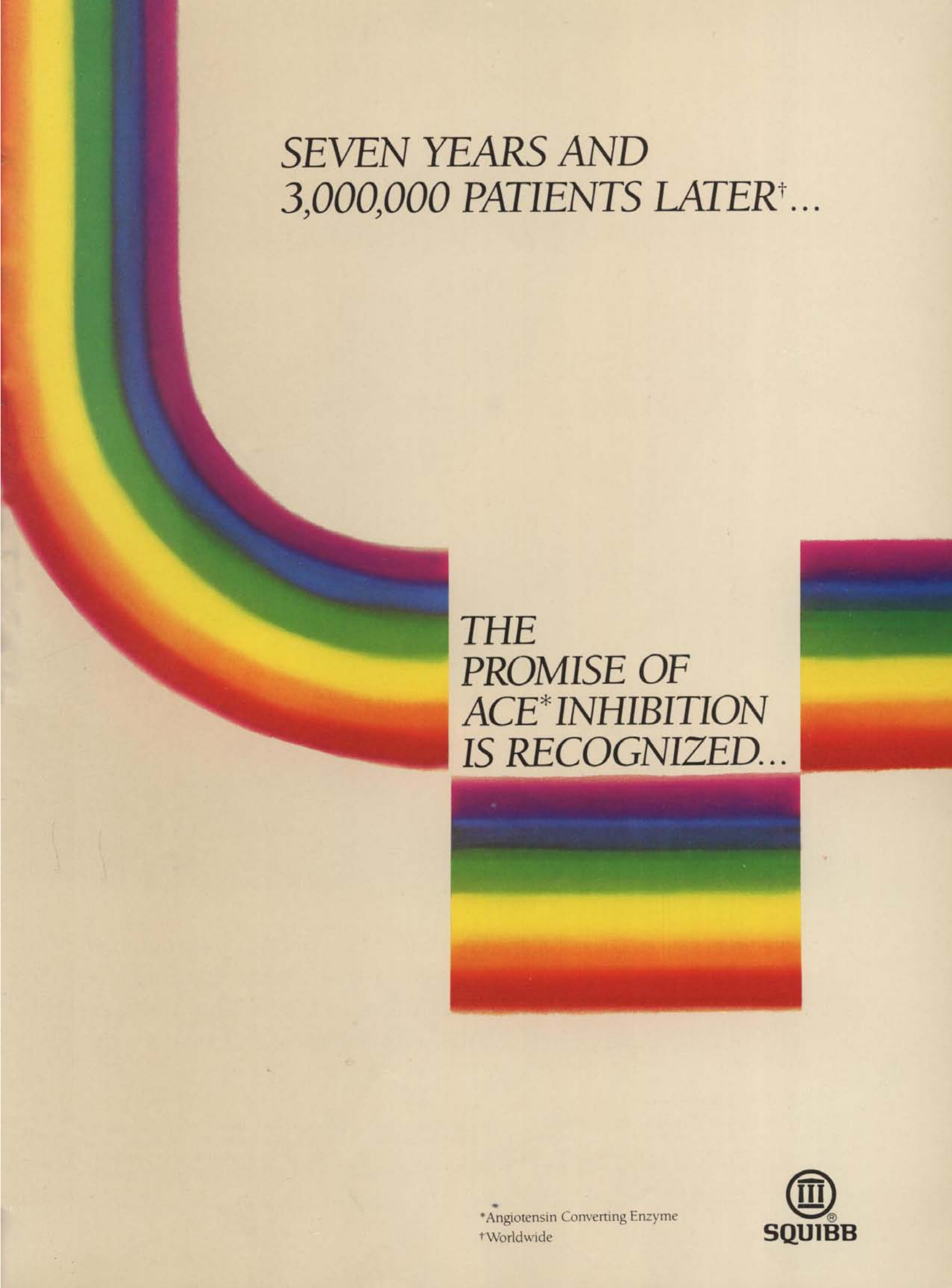
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INDICATIONS: Hypertension — CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal 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 hour 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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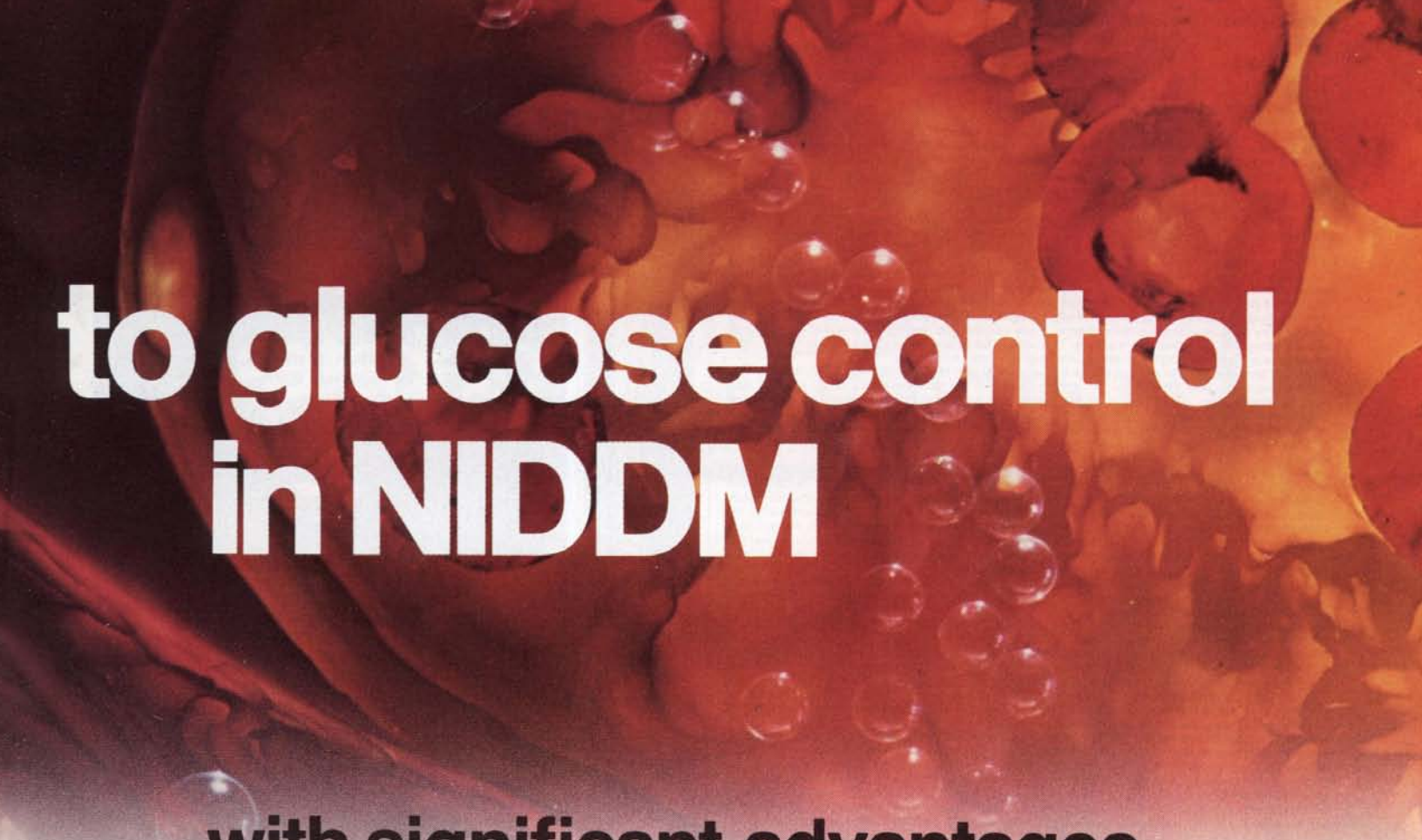

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Long-term metabolic improvement "Long-term therapy with glipizide, in contrast to studies of other sulfonylureas, often results in a sustained increase in glucose-stimulated insulin secretion."[3]

While controversy remains in the findings of the UGDP, there have been reports of increased cardiovascular risk associated with oral hypoglycemic therapy.

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GLUCOTROL® (glipizide) Tablets
Brief Summary of Prescribing Information

INDICATIONS AND USAGE: GLUCOTROL is indicated as an adjunct to diet for the control of hyperglycemia in patients with non-insulin-dependent diabetes mellitus (NIDDM, type II) after an adequate trial of dietary therapy has proved unsatisfactory.

CONTRAINDICATIONS: GLUCOTROL is contraindicated in patients with known hypersensitivity to the drug or with diabetic ketoacidosis, with or without coma, which should be treated with insulin.

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 2-1/2 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 GLUCOTROL 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: Renal and Hepatic Disease: The metabolism and excretion of GLUCOTROL may be slowed in patients with impaired renal and/or hepatic function. Hypoglycemia may be prolonged in such patients should it occur.

Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection, dosage and instructions are important to avoid hypoglycemia. Renal or hepatic insufficiency may increase the risk of 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 or people 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.

Loss of Control of Blood Glucose: A loss of control may occur in diabetic patients exposed to stress such as fever, trauma, infection or surgery. It may then be necessary to discontinue GLUCOTROL and administer insulin.

Laboratory Tests: Blood and urine glucose should be monitored periodically. Measurement of glycosylated hemoglobin may be useful.

Information for Patients: Patients should be informed of the potential risks and advantages of GLUCOTROL, of alternative modes of therapy, as well as the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including non-steroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents. *In vitro* studies indicate that GLUCOTROL binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to a clinical situation. Certain drugs tend to produce hyperglycemia and may lead to loss of control, including the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A 20-month study in rats and an 18-month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

Pregnancy: Pregnancy Category C: GLUCOTROL (glipizide) was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of GLUCOTROL. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well-controlled studies in pregnant women. GLUCOTROL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. GLUCOTROL should be discontinued at least one month before the expected delivery date.

Nursing Mothers: Since some sulfonylurea drugs are known to be excreted in human milk, insulin therapy should be considered if nursing is to be continued.

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

ADVERSE REACTIONS: In controlled studies, the frequency of serious adverse reactions reported was very low. Of 702 patients, 11.8% reported adverse reactions and in only 1.5% was GLUCOTROL discontinued.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

Gastrointestinal: Gastrointestinal disturbances, the most common, were reported with the following approximate incidence: nausea and diarrhea, one in 70; constipation and gastralgia, one in 100. They appear to be dose-related and may disappear on division or reduction of dosage. Cholestatic jaundice may occur rarely with sulfonylureas: GLUCOTROL should be discontinued if this occurs.

Dermatologic: Allergic skin reactions including erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about one in 70 patients. These may be transient and may disappear despite continued use of GLUCOTROL; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

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

Metabolic: Hepatic porphyria and disulfiram-like alcohol reactions have been reported with sulfonylureas. Clinical experience to date has shown that GLUCOTROL has an extremely low incidence of disulfiram-like reactions.

Miscellaneous: Dizziness, drowsiness, and headache have each been reported in about one in fifty patients treated with GLUCOTROL. They are usually transient and seldom require discontinuance of therapy.

OVERDOSAGE: Overdosage of sulfonylureas including GLUCOTROL can produce hypoglycemia. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours since hypoglycemia may recur after apparent clinical recovery. Clearance of GLUCOTROL from plasma would be prolonged in persons with liver disease. Because of the extensive protein binding of GLUCOTROL (glipizide), dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION: There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOTROL; in general, it should be given approximately 30 minutes before a meal to achieve the greatest reduction in postprandial hyperglycemia.

Initial Dose: The recommended starting dose is 5 mg before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg. Dosage adjustments should ordinarily be in increments of 2.5-5 mg, as determined by blood glucose response. At least several days should elapse between titration steps.

Maximum Dose: The maximum recommended total daily dose is 40 mg.

Maintenance: Some patients may be effectively controlled on a once-a-day regimen, while others show better response with divided dosing. Total daily doses above 15 mg should ordinarily be divided.

HOW SUPPLIED: GLUCOTROL is available as white, dye-free, scored diamond-shaped tablets imprinted as follows: 5 mg tablet—Pfizer 411 (NDC 5 mg 0049-4110-66) Bottles of 100; 10 mg tablet—Pfizer 412 (NDC 10 mg 0049-4120-66) Bottles of 100.

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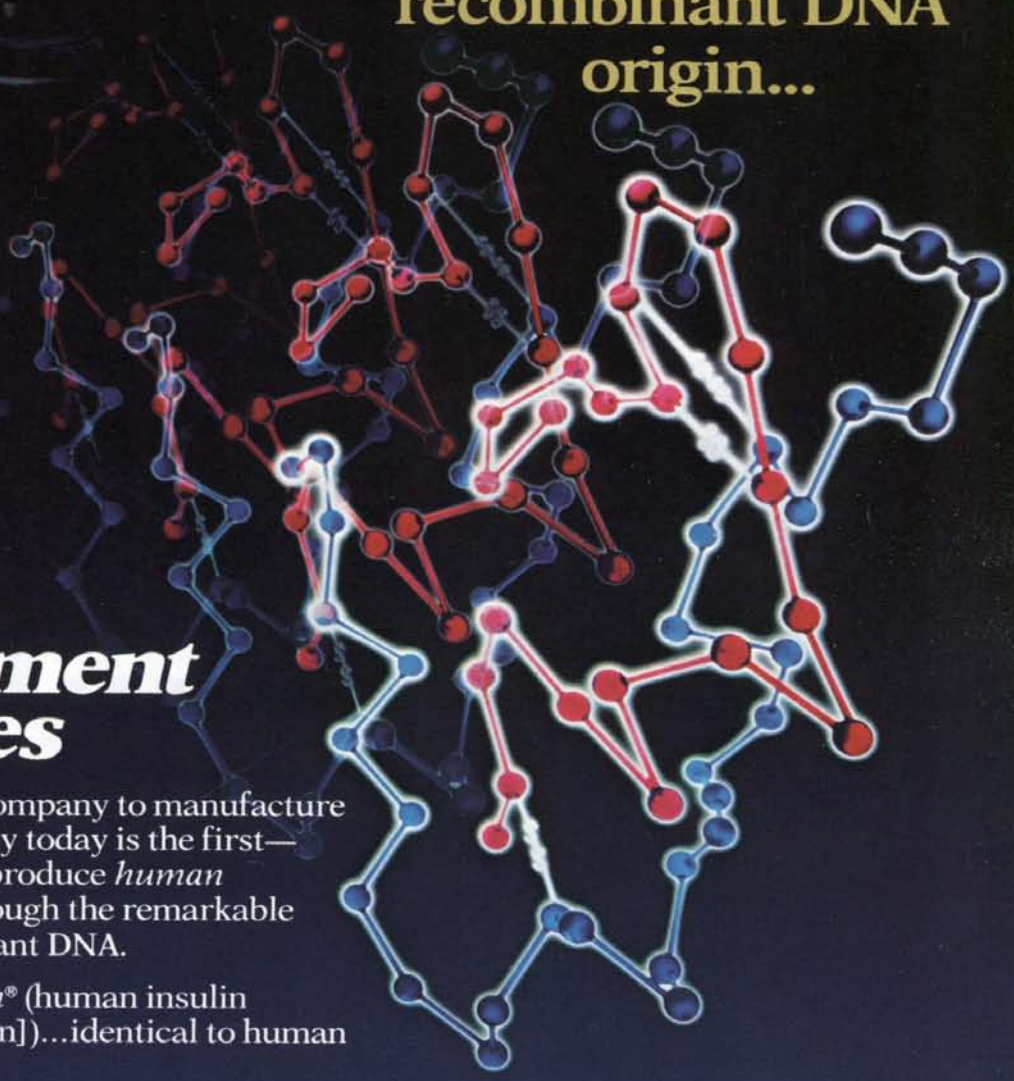

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