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diabetes

A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION®

RAPID PUBLICATIONS

DIAEAZ 35(2) 127–252 (1986)
ISSN 0012-1797

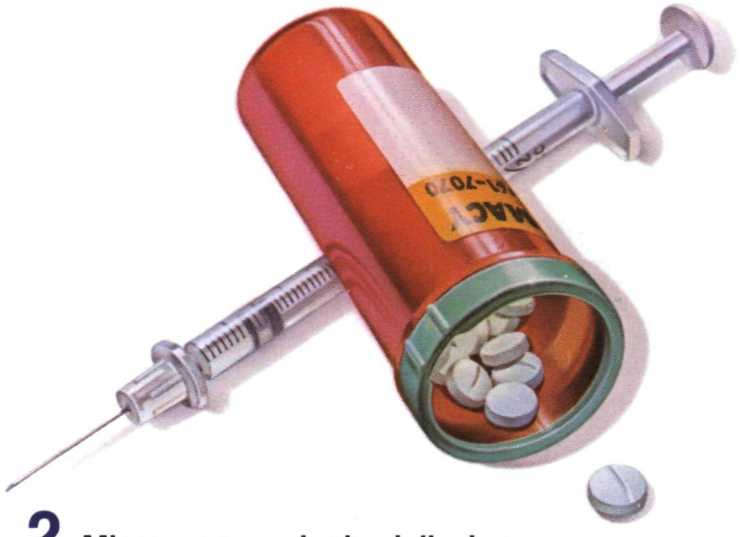
When a type II diabetic patient needs more than diet, unique MICRONASE® Tablets (glyburide) are a logical first choice.

Choosing antidiabetic

1. Micronase—a rational choice in type II diabetes

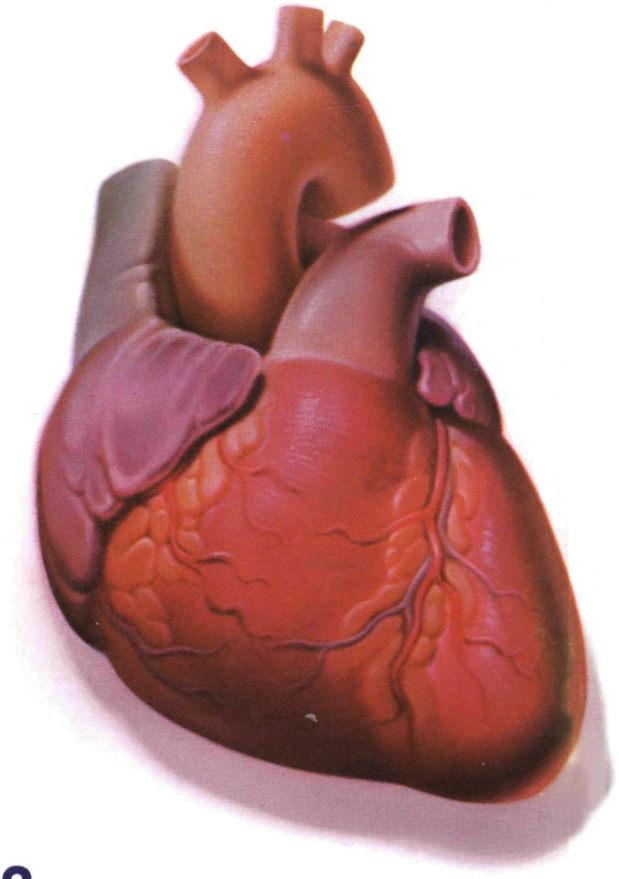
Insulin levels are normal or elevated in most patients with type II diabetes, although insulin action is markedly impaired. MICRONASE helps normalize the tissue response to endogenous insulin.

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.



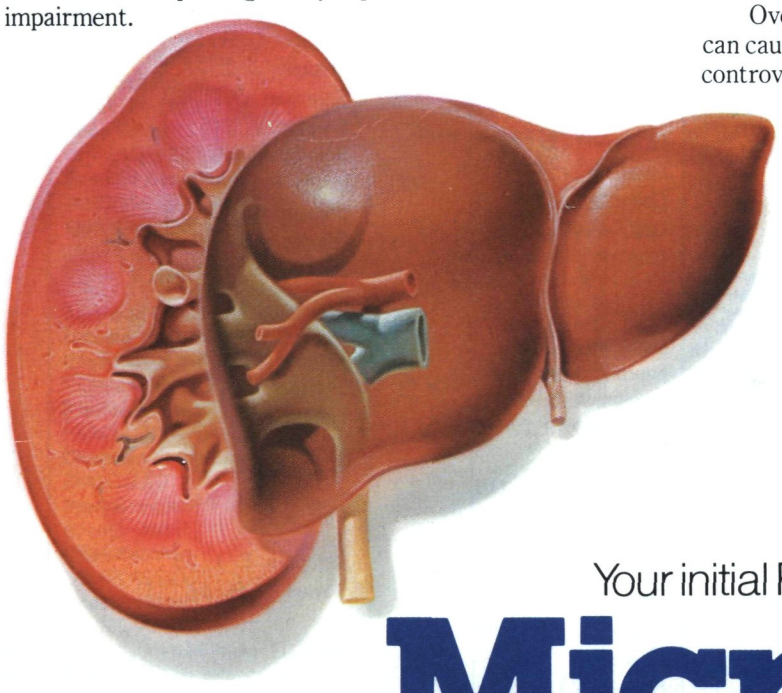
3. Micronase—for the type II diabetic patient who is also hypertensive: Control without risk of water retention

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.

FEBRUARY AUTHOR INDEX

(Volume 35, Number 2)

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.

In view of *The Copyright Revision Act of 1976*, all transmittal letters to the editor must contain the following language before manuscripts can be reviewed for possible publication: "In consideration of ADA's taking action in reviewing and editing my (our) submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to the ADA in the event that such work is published by the ADA. "We regret that transmittal letters not containing the foregoing language signed by all authors of the manuscript will necessitate return of your manuscript.

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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., National Service Center, 1660 Duke Street, Alexandria, Virginia 22314.

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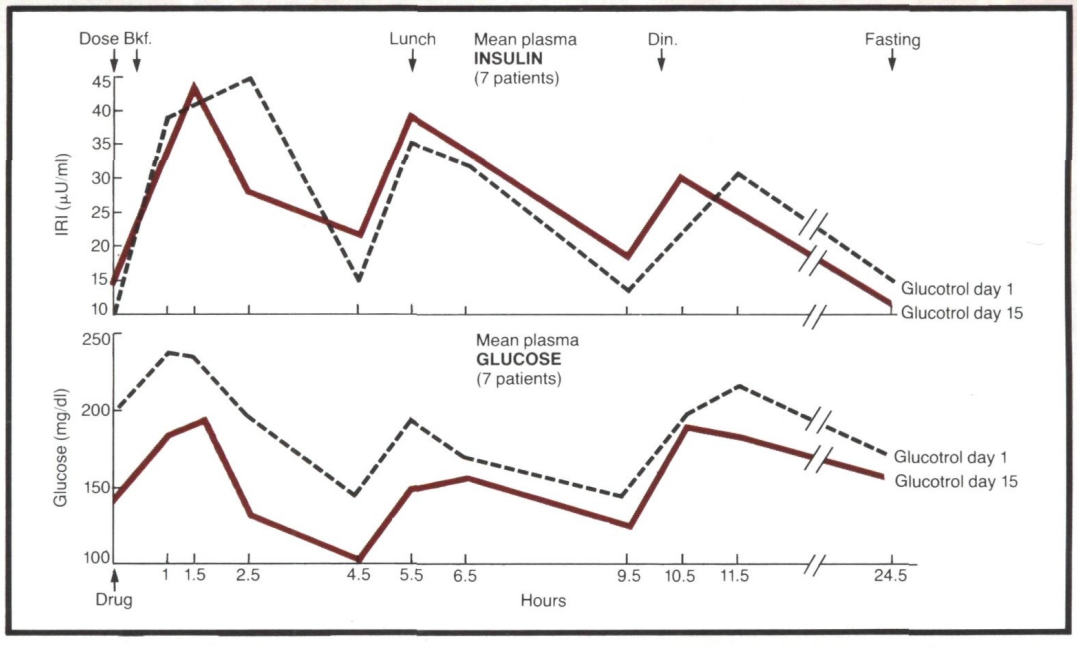
Glucotrol®
(glipizide) 5-mg and 10-mg Scored Tablets

Breaking barriers

more normal insulin release and utilization



(Adapted from Peterson CM, et al[1])

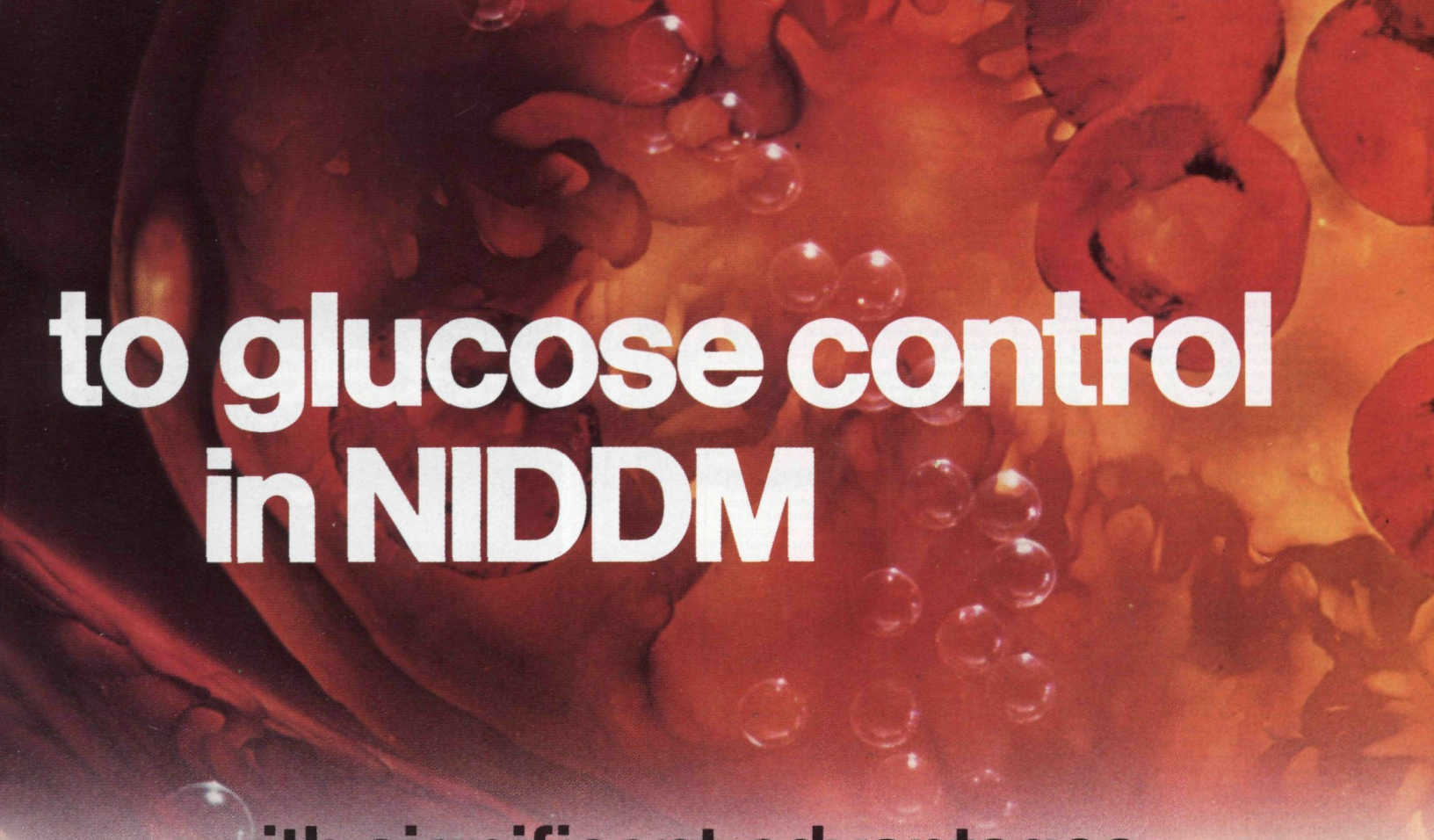
Glucose and insulin response to three standard meals was measured at eleven time points on the first and fifteenth days of administration of Glucotrol (glipizide) to seven patients with NIDDM. The mean dose of Glucotrol was 8.7 mg per day (0.1 mg/kg).

■ Insulin levels rose markedly after the first meal, then dropped, then rose again following subsequent meals.

■ The insulin response pattern with Glucotrol closely simulates the pattern commonly seen in nondiabetics.

References: 1. Peterson CM, Sims RV, Jones RL, et al: Bioavailability of glipizide and its effect on blood glucose and insulin levels in patients with non-insulin-dependent diabetes. *Diabetes Care* 1982; 5:497-500. **2.** Melander A, Wåhlin-Boll E: Clinical pharmacology of glipizide, in *Proceedings of a Symposium: New Perspectives in Noninsulin-Dependent Diabetes Mellitus and the Role of Glipizide in Its Treatment. Am J Med*, pp. 41-45, Nov. 30, 1983. **3.** Feinglos MN, Lebovitz HE: Long-term safety and efficacy of glipizide, in *Proceedings of a Symposium: New Perspectives in Noninsulin-Dependent Diabetes Mellitus and the Role of Glipizide in Its Treatment. Am J Med*, pp. 60-66, Nov. 30, 1983.

ROERIG Pfizer



to glucose control in NIDDM

with significant advantages for many NIDDM patients

Rapid, consistent therapeutic action "The aim of sulfonylurea treatment should be complete normalization of glucose economy... therefore, the sulfonylurea should be potent and rapid-acting. Moreover, it should have complete bioavailability in order to minimize variations between and within individual subjects.

"Glipizide [Glucotrol] has complete bioavailability and its absorption and onset of action are very rapid."[2]

Rapid excretion, inactive metabolites "As glipizide [Glucotrol] is very rapidly eliminated, and as there is no evidence that its metabolites are significantly active, the risk of long-lasting hypoglycemia should be small.... "[2] However, as with all sulfonylureas, hypoglycemia may occur.

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.

Glucotrol®

(glipizide) 5-mg and 10-mg Scored Tablets

When diet alone fails in non-insulin-dependent diabetes mellitus

Please turn page for Glucotrol® (glipizide) prescribing information.

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Organ of the European Association for the Study of Diabetes (EASD)

Volume 28 Number 11 November 1985

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INTRODUCING

The first proven for intermittent

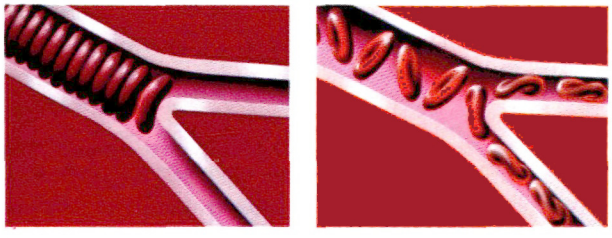
effective agent claudication:

AN IMPORTANT NEW CONCEPT IN 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.

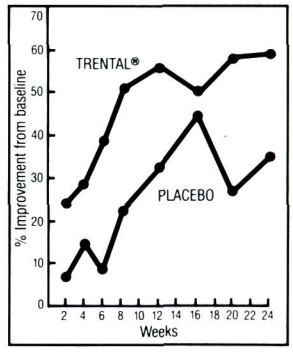


Trental® improves perfusion of ischemic tissue. Current evidence indicates that Trental® helps establish normal blood flow by lowering blood viscosity and by restoring erythrocyte flexibility.[2,3]

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: Although a causal relationship has not been established, there have been reports of bleeding and/or prolonged prothrombin time in patients treated with Trental® (pentoxifylline) with and without anticoagulants or platelet aggregation inhibitors. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration) should have periodic examinations for bleeding including hematocrit and/or hemoglobin. Trental® (pentoxifylline) has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, antidiabetic agents, and antiarrhythmics, without observed problems. Small decreases in blood pressure have been observed in some patients treated with Trental® (pentoxifylline); periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensive therapy. If indicated, dosage of the antihypertensive agents should be reduced.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies of the carcinogenic potential of pentoxifylline were conducted in mice and rats by dietary administration of the drug at doses up to approximately 24 times (570 mg/kg) the maximum recommended human daily dose (MRHD) of 24 mg/kg for 18 months in mice and 18 months in rats with an additional 6 months without drug exposure in the latter. No carcinogenic potential for pentoxifylline was noted in the mouse study. In the rat study, there was a statistically significant increase in benign mammary fibroadenomas in females in the high dose group (24 X MRHD). The relevance of this finding to human use is uncertain since this was only a marginal statistically significant increase for a tumor that is common in aged rats. Pentoxifylline was devoid of mutagenic activity in various strains of *Salmonella* (Ames test) when tested in the presence and absence of metabolic activation.

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

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

Pediatric Use: Safety and effectiveness in children below the age of 18 years have not been established.

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

The table summarizes the incidence (in percent) of adverse reactions considered drug related, as well as the numbers of patients who received controlled-release Trental® (pentoxifylline) tablets, immediate-release Trental® (pentoxifylline) capsules, or the corresponding placebos. The incidence of adverse reactions was higher in the capsule studies (where dose related increases were seen in digestive and nervous system side effects) than in the tablet studies. Studies with the capsule include domestic experience, whereas studies with the controlled-release tablets were conducted outside the U.S. The table indicates that in the tablet studies few patients discontinued because of adverse effects.

INCIDENCE (%) OF SIDE EFFECTS

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

Trental® (pentoxifylline) has been marketed in Europe and elsewhere since 1972. In addition to the above symptoms, the following have been reported spontaneously since marketing, or occurred in other clinical trials with an incidence of less than 1%; the causal relationship was uncertain: Cardiovascular—dyspnea, edema, hypotension; Digestive—anorexia, cholecystitis, constipation, dry mouth/thirst; Nervous—anxiety, confusion; Respiratory—epistaxis, flu-like symptoms, laryngitis, nasal congestion; Skin and Appendages—brittle fingernails, pruritus, rash, urticaria; Special Senses—blurred vision, conjunctivitis, earache, scotoma; and Miscellaneous—bad taste, excessive salivation, leukopenia, malaise, sore throat/swollen neck glands, weight change.

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

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

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

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

While the effect of Trental® (pentoxifylline) may be seen within 2 to 4 weeks, it is recommended that treatment be continued for at least 8 weeks. Efficacy has been demonstrated in double-blind clinical studies of 6 months duration.

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

Hoechst-Roussel Pharmaceuticals Inc.
Somerville, New Jersey 08876

Hoechst

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

Q7362-985

The Diabetes Research and Education Foundation, Inc. is soliciting grant requests for promising initiatives in the field of diabetes research and education. The Foundation is an independent, non-profit organization with a Board of Trustees comprised of specialists in diabetes research, clinical practice, pharmacy and patient education. The Board meets twice per year to review grant requests and disburse awards. Individual grant awards are currently limited to $20,000.

To be considered at the next meeting, which is scheduled for late April, grant applications must be received by March 15, 1986. Applications can be obtained by writing to:

Diabetes Research and Education Foundation, Inc.
P.O. Box 6168
Bridgewater, N.J. 08807-9998
ATTENTION: Herbert Rosenkilde, M.D., Executive Director

DO3003-186

Diabetes Editor

The American Diabetes Association invites applications for the editorship of the journal *Diabetes*.

The appointment is for three years, with a possible two-year extension. Editorship requires the availability of two to four Associate Editors located in the same city or preferably the same institution.

Interested parties should submit a letter of intent by *March 1, 1986*. Curriculum vitae of the applicants for Editor and Associate Editors should be included. Further instructions will follow upon receipt of the letter of intent.

Please address correspondence to:

Dean H. Lockwood, MD
Box 693
University of Rochester
Medical Center
Rochester, NY 14642

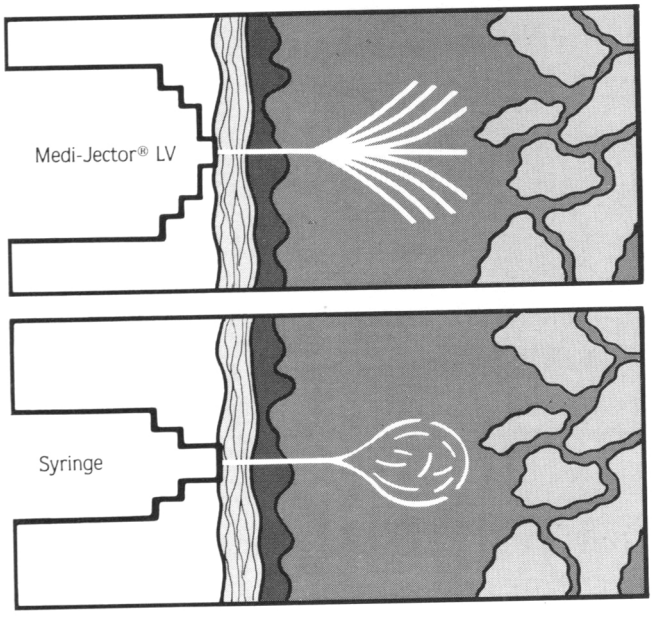
Your patients may not have a choice about taking insulin.

They should have a choice about how they take it.

"It's not so bad; you'll get used to the needle."

What else could you tell the diabetic who must take insulin? After all, taking insulin is life-sustaining to many, while for others it is the best way to control blood sugar and retard or prevent life-threatening complications. Your challenge is to obtain maximum compliance, for effective control.

The reality, however, is that puncturing the skin with a needle is neither normal nor something to look forward to with anything but resignation, and for various psychosocial or physical reasons something that can be painful.



Even patients must tell themselves, "It's not so bad."

How else could they cope with up to 1,000 punctures a year? How many of your patients would rather live without needle injections and still have the maximum benefit of insulin therapy?

Medi-Jector® Needleless Injection: a better choice for compliance, control and comfort.

The development of Medi-Jector's needleless injection technology has paralleled the evolution of modern diabetes management, with its goal of improved control facilitated by self blood glucose monitoring and multiple daily doses of insulin.

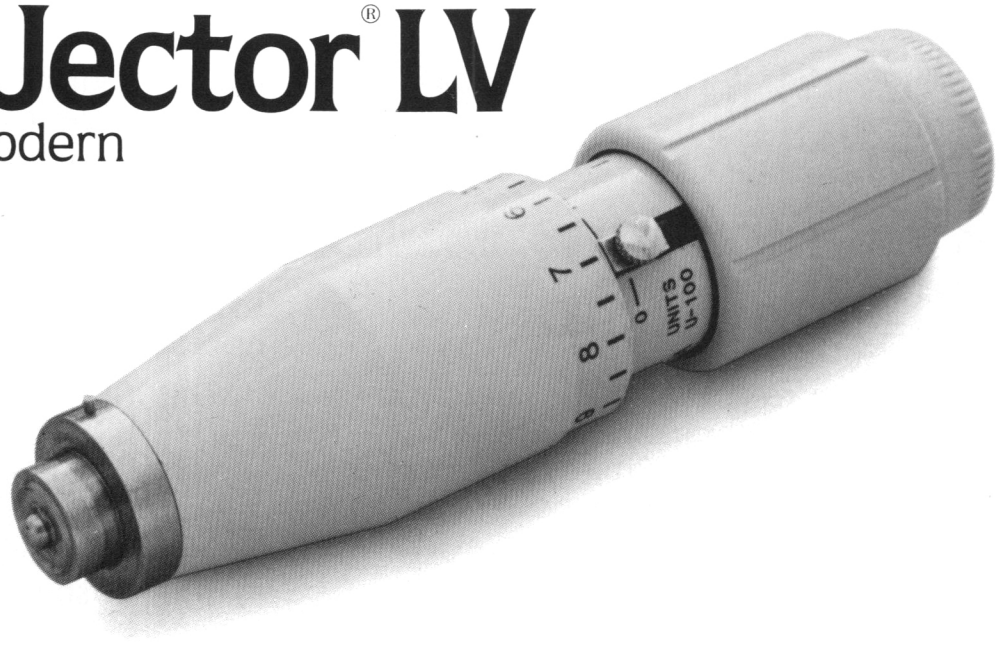
The prospect of multiple daily injections cannot be pleasant for patients who have found one shot a day to be painful, or for patients who have never taken insulin before. Such fear of needle punctures can result in a detrimental compliance problem.

Medi-Jector is a precision, mechanically-powered injection device, proven in over seven years of patient use by thousands of diabetics.

Medi-Jector forces insulin, under pressure, through a tiny orifice which produces a liquid column that is **one-third** the size of the smallest needle. After penetration, the insulin is rapidly dispersed through the planes of least resistance as a fine spray. Penetration depth is adjustable to accommodate individual and site-to-site variation in skin resistance. Nothing touches the patient but the tiny column of insulin. Compared to needle injections, there is less tissue trauma, greater insulin dispersion and improved absorption. Most important, the injection sensation is virtually undetectable.

Medi-Jector users tell us they could no longer conceive of taking multiple injections with a needle, and most say they never want to "see" an insulin syringe again.

New
Medi-Jector® LV
designed for modern insulin therapy



Derata Corporation, a pioneer in the research and development of insulin jet injector systems, designed its third generation system to meet the needs of modern multiple insulin injection therapy.

Medi-Jector LV delivers up to 50 units of U-100 (single or mixed doses) with unequaled comfort. Confirmed accuracy (tenths of a unit) delivers precise doses, time after time.

Its compact size (6 inches long) and light weight (12 ounces) provides anywhere, anytime convenience.

Simple operation and available training materials makes patient instruction easy and effective. Continuing customer support services ensure patient confidence and maximum utilization.

Medi-Jector LV is classified as durable medical equipment and is 80% to 100% covered by many insurance plans. Additionally, the Derata Corporation is so confident of the quality and comfort of the Medi-Jector LV that it is sold with a prorated money-back guarantee and warranteed for five years. Medi-Jector LV will provide your patients years of economical, effective insulin delivery with a comfort unequaled by insulin syringes.

Wouldn't your patients appreciate the opportunity to compare Medi-Jector LV with the needle, and then choose? Show them the modern alternative, then let them choose.

Discover why your patients deserve to have the Medi-Jector choice — call us at 1-800-328-3074. We will provide you with complete information and the name of your local distributor.

P-10185

DERATA
CORPORATION

7380 32nd Avenue North
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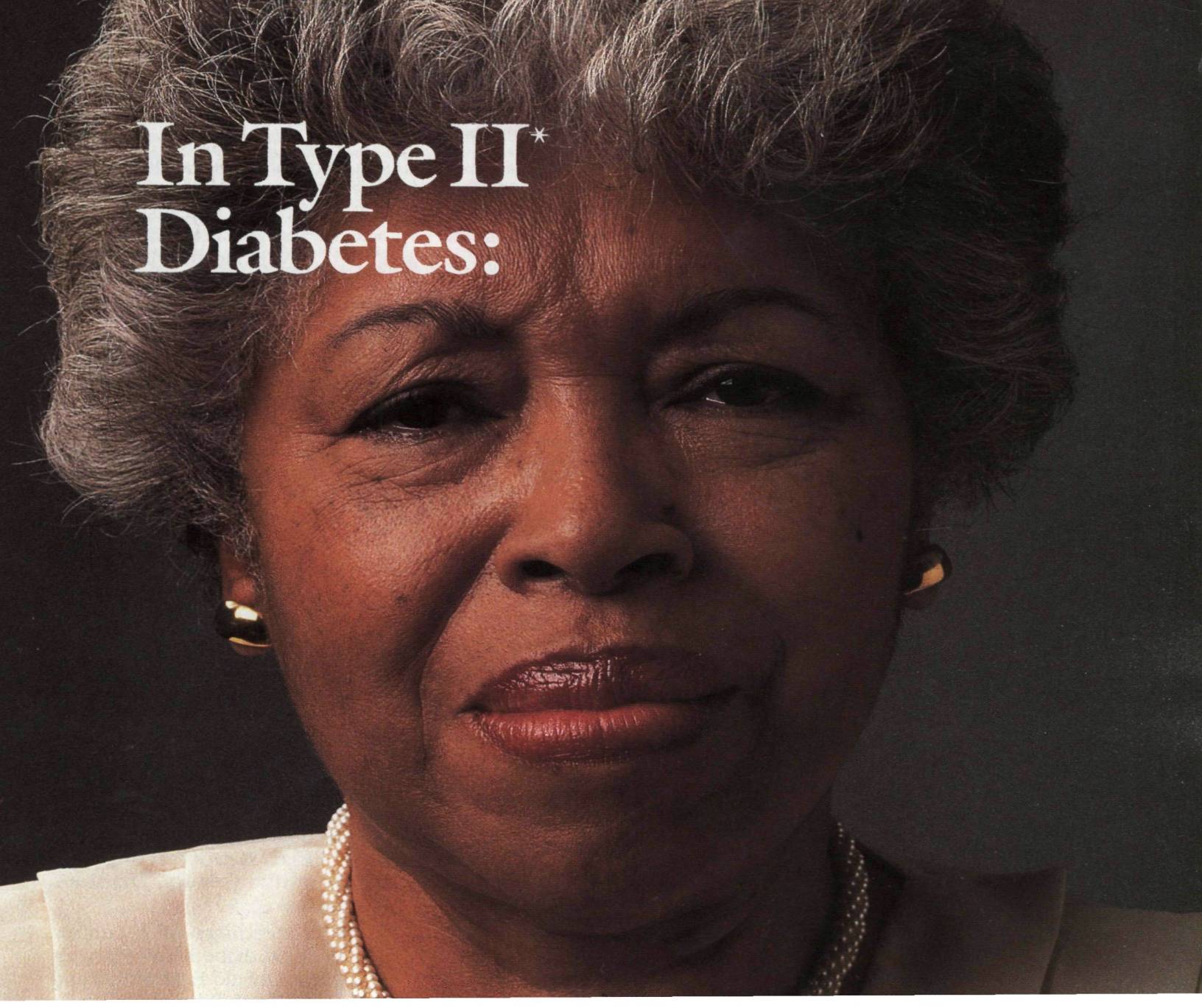
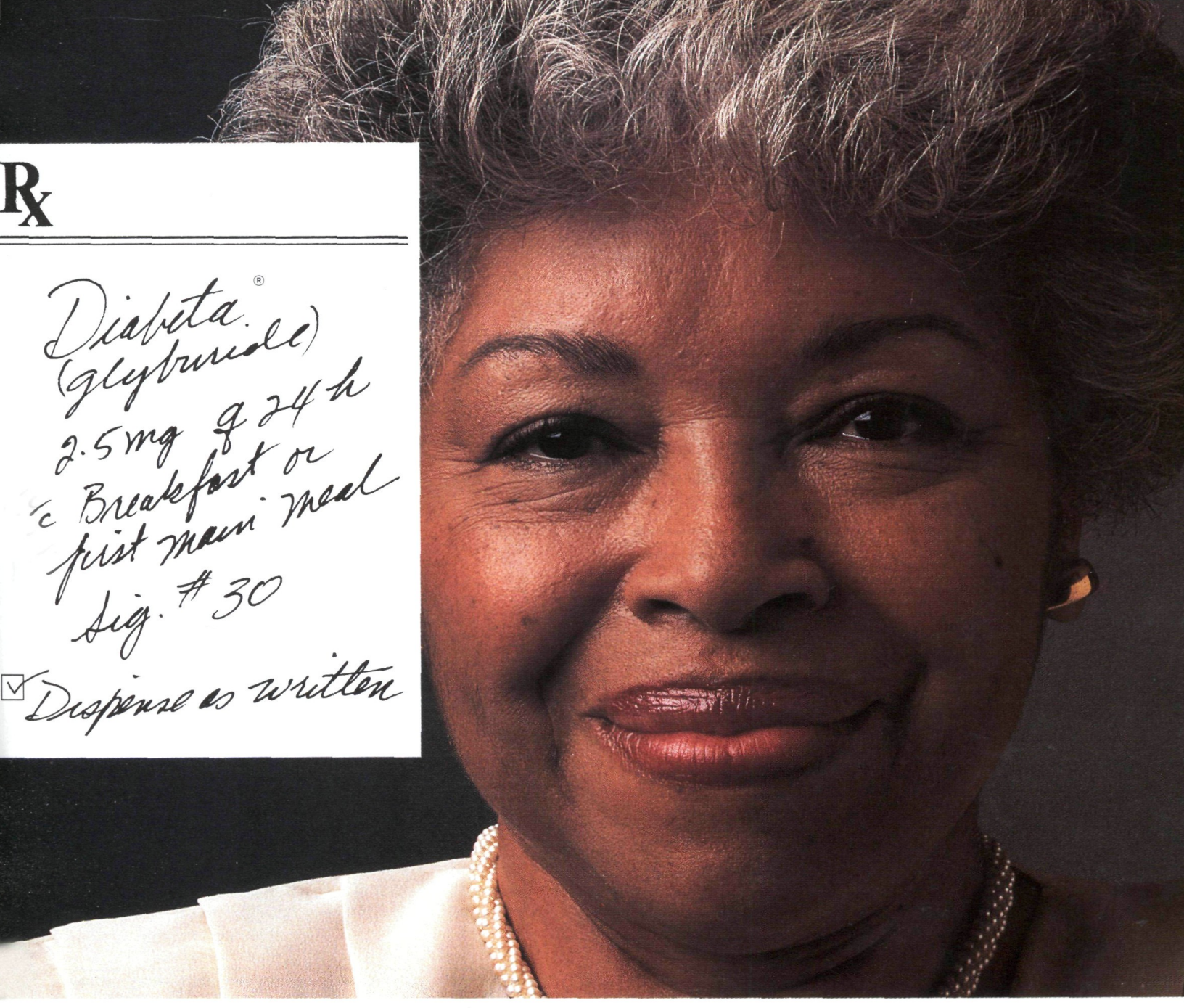


When persistent hyperglycemia or adverse effects signal the need for a change—

*Non-insulin-Dependent Diabetes Mellitus (NIDDM)

Although the findings are controversial, the UGDP study reported in 1970 that the use of tolbutamide, an oral sulfonylurea, was associated with increased cardiovascular risk.



Consider the world's most prescribed oral hypoglycemic agent:

Control: High success rate** (77%-100%) reported in Type II diabetics who fail on diet alone.

Effective in some patients who fail on other oral agents.

Compliance: Simple one-a-day dosage regimen for most patients.

Low incidence of side effects.

Confidence: Safety proven in over 15 years of clinical use.

DIET &

Diaβeta® TABLETS 1.25, 2.5 and 5mg

(GLYBURIDE)

**Data on file, Hoechst-Roussel Pharmaceuticals Inc.

See following page for brief summary of prescribing information.

Hoechst-Roussel Pharmaceuticals Inc.
Somerville, New Jersey 08876

Hoechst

THE WORLD'S MOST PRESCRIBED ORAL HYPOGLYCEMIC AGENT

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.

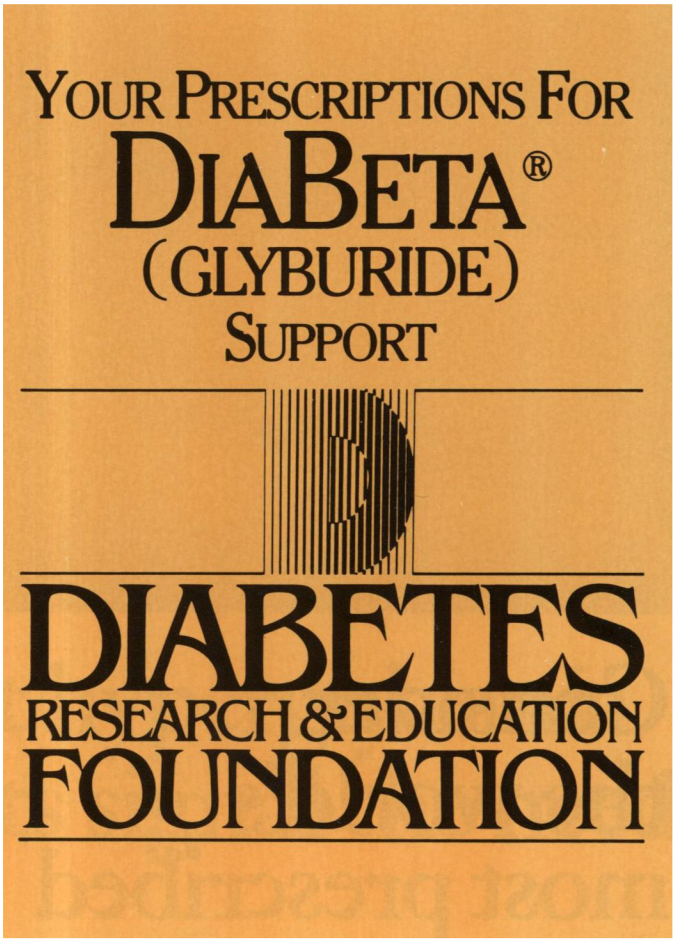
Dermatologic Reactions: Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in 1.5% of treated patients. These may be transient and may disappear despite continued use of DiaBeta® (glyburide); if skin reactions persist, the drug should be discontinued.

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.



Hoechst-Roussel Pharmaceuticals Inc.
Somerville, New Jersey 08876

Hoechst

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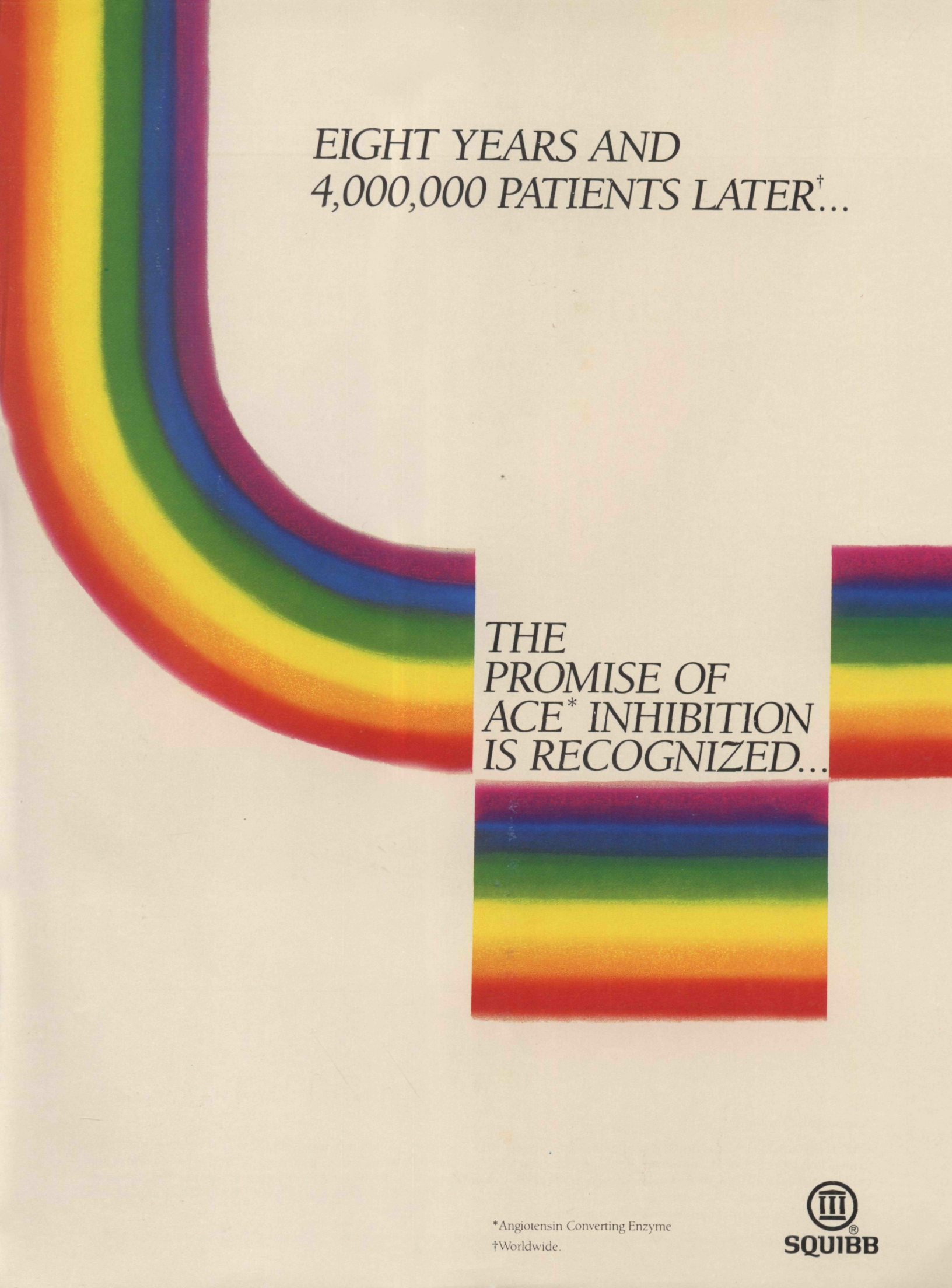

*Angiotensin Converting Enzyme
†Worldwide.

SQUIBB®

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

*Angiotensin Converting Enzyme

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

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

Expanded Prescribing Freedom—
Mild-to-Moderate Hypertension

Capoten for Initial Therapy of Hypertension†

- ☐ Fatigue, loss of libido, impotence, and mental impairment almost never occur‡
- ☐ Effective alone or in combination with diuretics
- ☐ Convenient bid dosage

ACE*INHIBITOR

CAPOTEN®
(captopril tablets)

FIRST-LINE THERAPY THAT PUTS QUALITY OF LIFE FIRST

CAPOTEN® TABLETS
Captopril Tablets

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

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

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia ($<1000/mm^3$) 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 vascular 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 usually 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 $<1000/mm^3$) 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 and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, 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. (J3-658D)

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.

SQUIBB®

INNOVATORS IN CARDIOVASCULAR MEDICINE

526-553 Issued: January 1986

AMERICAN DIABETES ASSOCIATION HAS MOVED TO ALEXANDRIA, VIRGINIA

In order to serve ADA's constituency more effectively and to carry out the mission of the Association, ADA has moved its National Service Center from New York City to Alexandria, Virginia.

Mail to ADA should be addressed to:

American Diabetes Association, Inc.
National Service Center
1660 Duke Street
Alexandria, VA 22314
Phone: (800) ADA-DISC
(703) 549-1500


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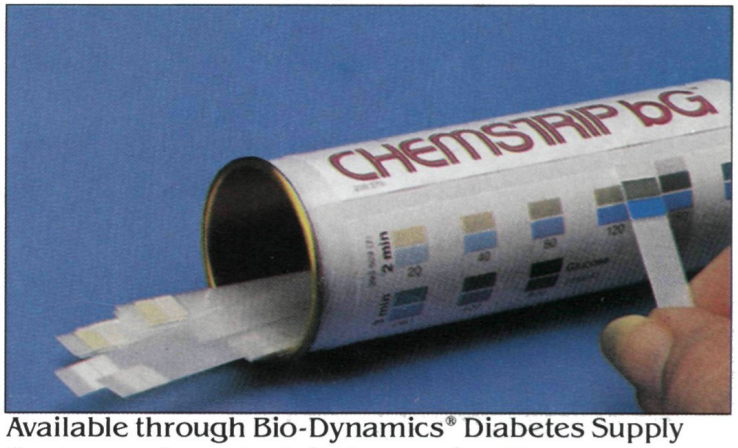

Available through Bio-Dynamics® Diabetes Supply Centers and most retail pharmacies. For more information, call 1-800-858-8072.

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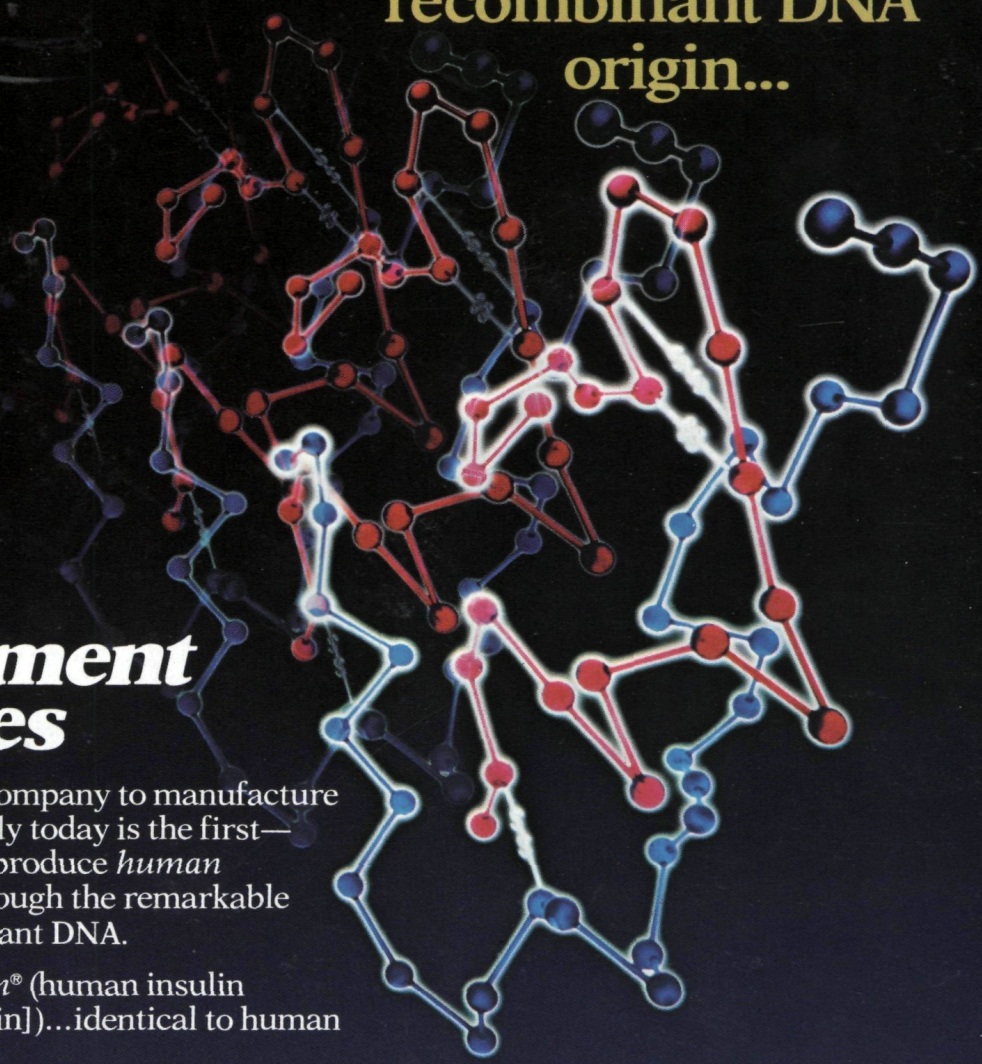
Bio-Dynamics Division
9115 Hague Road, Indianapolis, IN 46250

From the first commercially produced insulin...

to the first human insulin of recombinant DNA origin...



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Lilly offers diabetic patients the most complete line of insulins—23 formulations in all—including Humulin and all forms of Iletin® (insulin).

Moreover, Lilly has the widest retail distribution of insulin in the United States, which assures your patients—wherever they may be—availability of Humulin or Iletin.

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Even with the achievement of Humulin, Lilly research continues to strive to develop new products and improved insulin delivery systems for better diabetes care.

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IN DIABETES CARE

Lilly

Eli Lilly and Company
Indianapolis, Indiana 46285

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

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