VOLUME 13 NUMBER 4 APRIL 1990

# DIABETES CARE®

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION



American Diabetes Association®

ISSN 0149-5992

A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION

In non-insulin-dependent diabetes...

# BREAKFAST-TO-BREAKFAST CONTROL...*One dose a day.*

Upjohn

## 24-hour glycemic control can begin at the breakfast table.

When diet and exercise aren't enough, once-a-day MICRONASE provides 24-hour control of both postprandial and fasting blood glucose levels. The usual starting dosage, 2.5 mg to 5 mg once a day, should be taken with breakfast or the first main meal of the day. Some patients, particularly those receiving more than 10 mg daily, may have a more satisfactory response with twice-a-day dosage.

All sulfonylureas, including MICRONASE, can cause severe hypoglycemia. Proper patient selection, dosage, and instructions are important.

# Micronase®

Tablets (glyburide) **Usual starting dosage 2.5 mg-5 mg once a day**

Please see adjacent page for brief summary of prescribing information.

## APRIL AUTHOR INDEX
(Volume 13, Number 4)

VOLUME 13 NUMBER 4
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# DIABETES CARE®

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION



## Mission Statements for *Diabetes Care* and *Diabetes*

***Diabetes Care* publishes original articles and reviews of human and clinical research intended to increase knowledge, stimulate research, and promote better management of people with diabetes mellitus. Emphasis is on human studies reporting on the pathophysiology and treatment of diabetes and its complications; genetics; epidemiology; psychosocial adaptation; education; and the development, validation, and application of accepted and new therapies. Topics covered are of interest to clinically oriented physicians, researchers, epidemiologists, psychologists, diabetes educators, and other professionals.**

***Diabetes* publishes original research about the physiology and pathophysiology of diabetes mellitus. Submitted manuscripts can report any aspect of laboratory, animal, or human research. Emphasis is on investigative reports focusing on areas such as the pathogenesis of diabetes and its complications, normal and pathologic pancreatic islet function and intermediary metabolism, pharmacological mechanisms of drug and hormone action, and biochemical and molecular aspects of normal and abnormal biological processes. Studies in the areas of diabetes education or the application of accepted therapeutic and diagnostic approaches to patients with diabetes mellitus are not published.**

All manuscripts and other editorial correspondence should be sent by first class mail to David C. Robbins, MD, Editor, *Diabetes Care*, University of Vermont, Department of Medicine, Metabolic Unit, Given C-352, Burlington, VT 05405. Manuscripts and correspondence regarding review articles should be sent to Ralph A. DeFronzo, MD, Review Editor, *Diabetes Care*, Department of Medicine, Division of Diabetes, UT-HSCSA, 7703 Floyd Curl Drive, San Antonio, TX 78284.

*Diabetes Care* publishes only original material. When submitting a manuscript, authors must state in their transmittal letter that the material has not been previously published or is not currently being submitted to another journal.

Manuscripts should be prepared in accord with the requirements specified in the document "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," *Annals of Internal Medicine* 96:766–71, 1982. An "Information for Authors" page containing specifications for manuscript preparation appears in the January and June issues of each volume.



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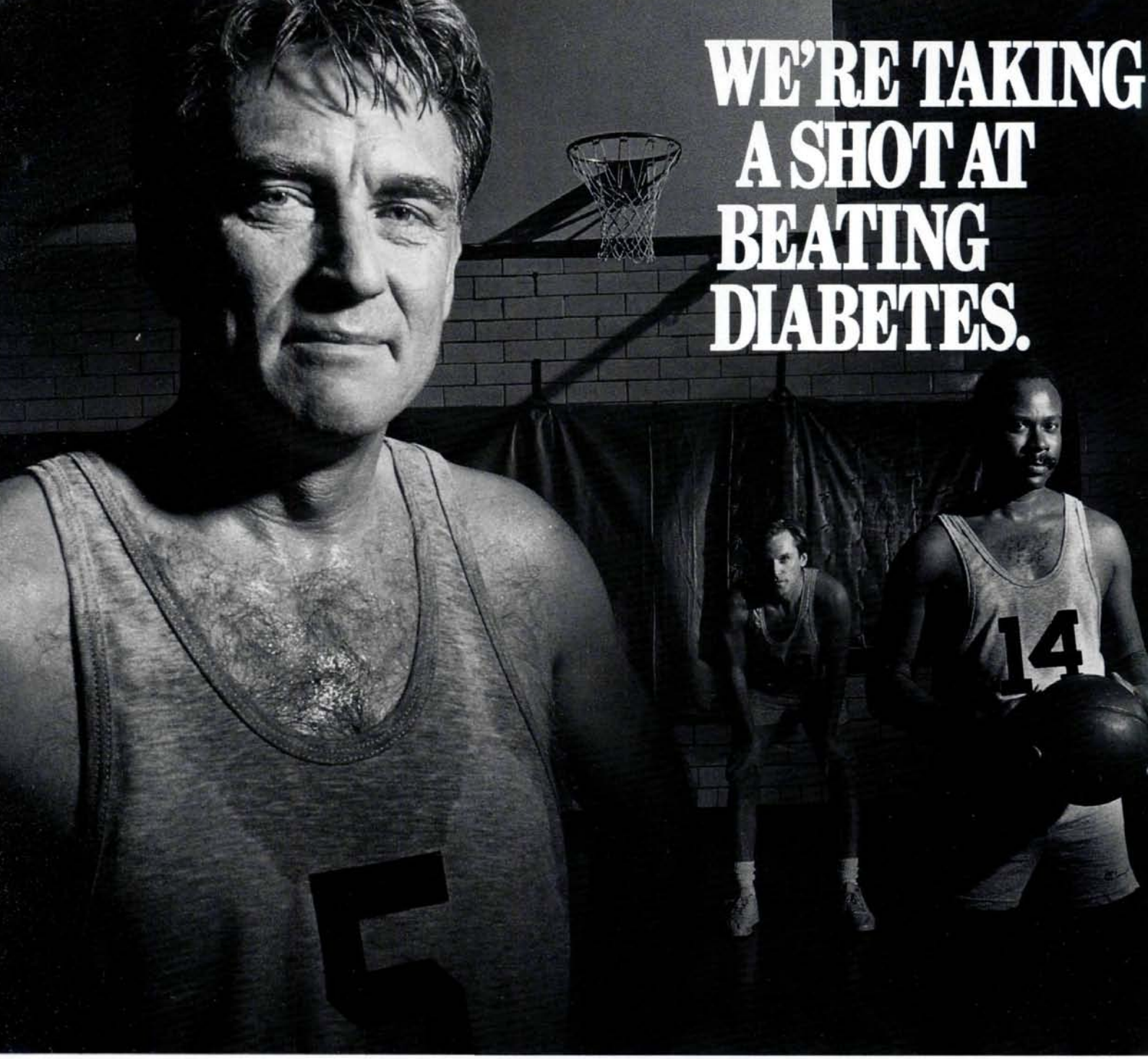
*Diabetes Care* is listed in *Science Citation Index, Current Contents/Life Sciences, Current Contents/Clinical Medicine, SCISEARCH, ISI/BIOMED* databases, and *Automatic Subject Citation Alert. Diabetes Care* is available online on *BRS Colleague*. For more information call 800-468-0908. It is also available in machine-readable format from University Microfilms International. *Diabetes Care* is printed on acid-free paper starting with Vol. 11(1), 1988.




# But we need you to win.


Teamwork. Without it, winning is impossible. That's why at Boehringer Mannheim we're joining the American Diabetes Association in their struggle to beat diabetes. But we need your support to make a difference.

Right now, when your patients with diabetes buy any Boehringer Mannheim self blood glucose monitoring product, we'll make a contribution to the ADA for diabetes research. It's that simple. Recommend a quality Boehringer Mannheim product, and help support the team that's taking a shot at beating diabetes.

**To learn how the ADA can help you further—call 1-800-232-3472.**

Teaming up against diabetes

American Diabetes Association.

BOEHRINGER MANNHEIM DIAGNOSTICS

Contribution to The ADA Research Program with purchase.

# IN THIS ISSUE

## Intensive Insulin Treatment in NIDDM: Windfall or Fiasco?

The value of self-monitoring of blood glucose (SMBG) for patients with insulin-dependent diabetes mellitus is well established. However, the potential benefits of an intensified treatment program for insulin-requiring patients with non-insulin-dependent diabetes mellitus (NIDDM) have not been adequately addressed. Floyd et al. (p. 386) constructed an algorithm for NIDDM patients to self-adjust insulin dosages based on SMBG values. There was good adherence to the program and improved diabetic control. Both treatment and control groups gained a similar amount of weight. These results indicate that intensification of insulin treatment in conjunction with SMBG may be feasible and useful in the treatment of this subgroup of patients with NIDDM.

## High-Tech Diabetes Management: A Simulation

Diabetic patients who adjust their own insulin must combine glucose monitoring with factors such as diet and exercise to estimate the proper insulin dosage for any given day. This scheme demands sophisticated accurate algorithms so that patients can make the necessary adjustments in dosage. Albisser et al. (p. 393) tested a new adjustment algorithm in a computer-simulation study that used urine and blood glucose determinations. The scheme successfully improved metabolic control in the simulated subjects and worked equally well with blood or urine glucose values. Furthermore, computer simulations such as these can provide researchers with valuable information regarding safety and efficacy before commencement of clinical studies.

## Exercising Questions for Native Americans

Biological evidence indicates that physical activity benefits individuals with non-insulin-dependent diabetes mellitus (NIDDM). Although activity questionnaires are widely used to conduct epidemiological research on the effects of physical exercise on diabetes, existing questionnaires are not appropriate for Native American populations with NIDDM. As part of the prospective Pima Indian Study of Arizona, Kriska et al. (p. 401) developed a questionnaire specifically geared to this population. It encompasses both leisure and occupational activities over the past week, past year, and lifetime. It is reproducible, and the validity of the current-activity section was confirmed by activity monitors in the field. This questionnaire should be a useful tool for studying the effects of physical exercise in Pima Indians and other Native American populations.

## To Test or Not to Test

How often do physicians order a blood glucose test in conjunction with an office visit for their patients with diabetes? Harris (p. 419) reports results from a national sample of 2879 physicians who care for diabetic patients. People with diabetes saw their physicians ~3 times/yr; a blood glucose test was ordered at ~70% of visits. This frequency was uninfluenced by type of therapy, age, race, or sex of the patient. Physicians nationwide requested the test with equal frequency, although doctors practicing alone were less likely to order it than those in partnership or group practice. Physicians seeing patients specifically for diabetes were more likely to request a blood glucose test. These results suggest that most doctors order blood glucose tests for their diabetic patients, but the frequency of testing may be influenced by the reason for the visit and how busy the doctor is.

# One out of every two men with diabetes will become impotent after age 50.

A statistical fact of life, yes.
But there is a solution. And it does not involve surgery.

**Visit us at the ADA Meeting in Atlanta**
**Booth #352**

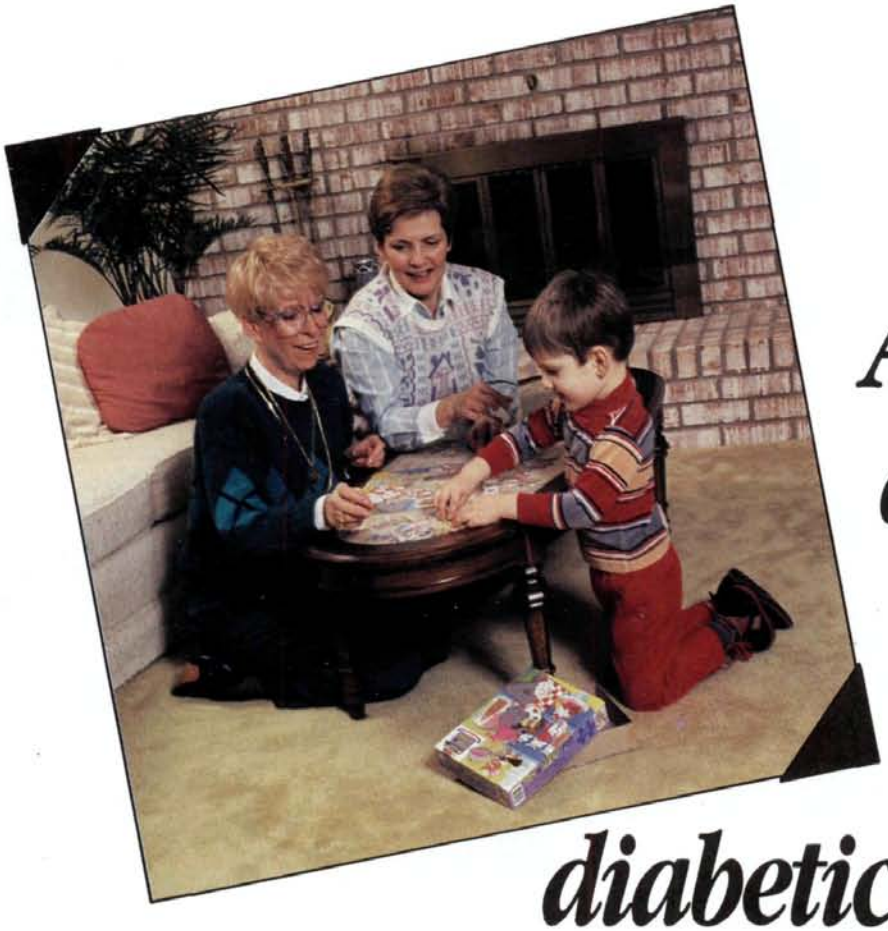
# ErecAid System®

## The most widely prescribed non-surgical solution for managing diabetes-induced impotence.

A 1988 market research study found that diabetes was the leading cause of impotence among ErecAid System owners. When queried, over 95% of diabetic men who used ErecAid System stated they would recommend it as safe and effective. In simple terms, ErecAid System works for a category of men whose impotence can be difficult to treat. And it works without surgery. The next time you diagnose impotence secondary to diabetes, prescribe ErecAid System. It may be the *only step* your patient will ever have to take to treat his impotence. For information about ErecAid System and the special support provided to physicians and patients, contact Osbon Medical Systems: 1-800-344-9688, Dept. 56.

**ErecAid System®**

*The leading choice for impotence management*



# *Are you doing all you can for your diabetic patients?*

*If your patient has blood glucose above 250 mg/dl, are you monitoring for DKA, diabetic ketoacidosis?*

Now GDS has a colorimetric test that allows you to detect "true" ketoacidosis.

The test:

- measures quantitatively, $\beta$-hydroxybutyrate, a major ketoacid, in serum or plasma
- can be performed in your laboratory or emergency rooms in minutes
- can also be used for monitoring the recovery of the patient from DKA

GDS

**GDS Diagnostics** Division of GDS Technololgy, Inc.
25235 Leer Drive P.O. Box 473 Elkhart, IN 46515 (800) 545-4GDS
Office: (219) 264-7384 Fax: (219) 262-0109

# When post-meal blood sugar demands control, demand Glucotrol

After meals, when NIDDM patients need insulin most, Glucotrol stimulates insulin release within minutes to control blood sugar.[1]

- When fasting, insulin levels return to basal levels[2]
- No deleterious effect on lipids[3]
- Low incidence of prolonged and severe hypoglycemia[4]

# Glucotrol®

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

When diet alone fails in non-insulin-dependent diabetes mellitus (NIDDM)

*As with all sulfonylureas, hypoglycemia can occur.*

*Please see brief summary of GLUCOTROL® (glipizide) prescribing information on next page.*


**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. Goebel R, Leb G: Effects of glyburide and glipizide on levels of immunoreactive insulin and blood sugar, in *Glipizide: A Worldwide Review*. Princeton, NJ, Excerpta Medica, 1984, pp 9-15. 3. Reaven GM: Effect of glipizide treatment on various aspects of glucose, insulin, and lipid metabolism in patients with noninsulin-dependent diabetes mellitus. *Am J Med* 1983;75(November 30):8-14. 4. Berger W, Caduff F, Pasquel M, et al: The relative frequency of severe sulfonylurea hypoglycemia in the last 25 years in Switzerland. *Schweiz Med Wochenschr* 1986;116:145-151.

**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 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. *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. A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known.

***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.

**Endocrine Reactions:** Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with this and other sulfonylureas.

**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, 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.

**CAUTION:** Federal law prohibits dispensing without prescription.

**More detailed professional information available on request.**

Pfizer

Roerig

ames

# The new Glucometer® 3

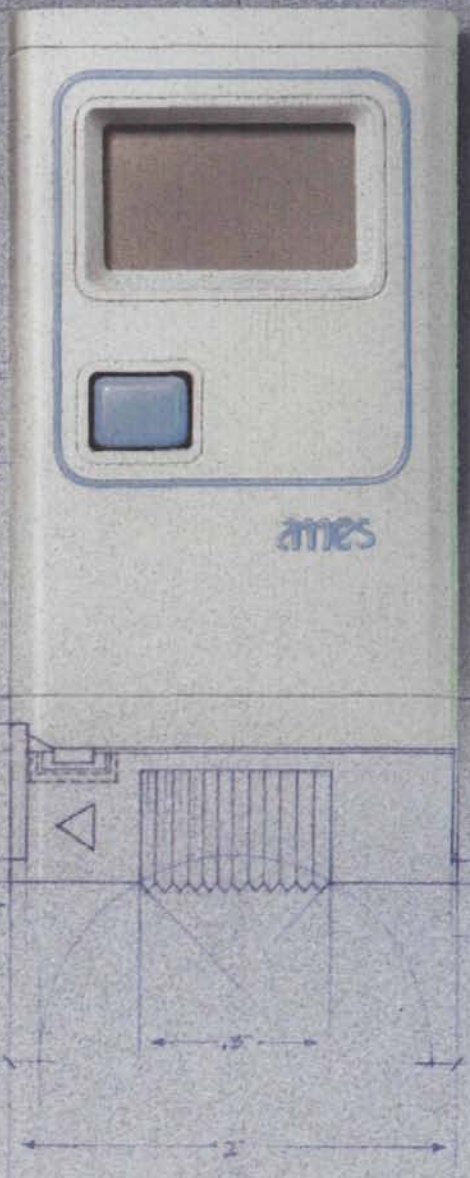
## Diabetes Care System

ames

# and the facts behind it.

## Presenting *all* sides of the story.

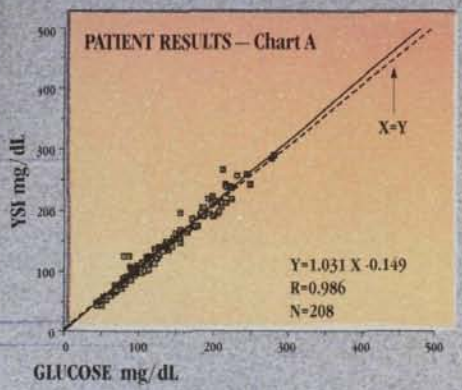
Making the right recommendation about a blood glucose monitoring system demands *all* the facts... the whole story of reliability and ease of use. Here are the facts about the new GLUCOMETER® 3 Diabetes Care System and GLUCOFILM™ Test Strips. Facts that clearly make it the right system for more patients.

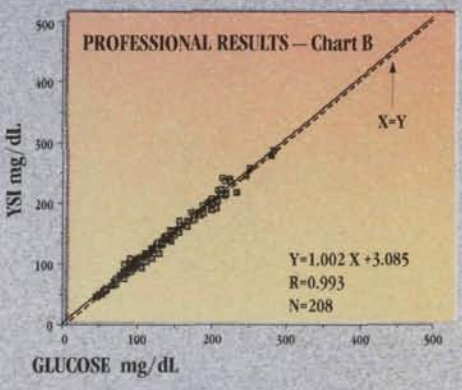



## Fact: Provides the accuracy you need to assure good diabetes management.

The GLUCOMETER 3 System assures you of clinically useful blood glucose results from 20-500 mg/dL.

The graphics shown demonstrate the close correlation of GLUCOMETER 3 System readings to YSI whole blood glucose values across a broad range.



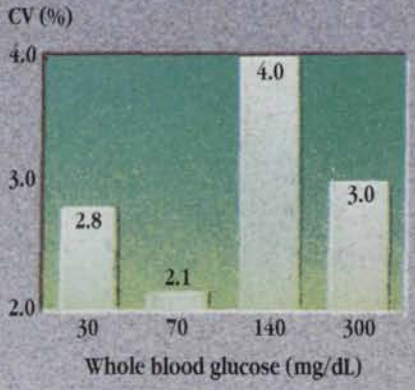



## Fact: Simplicity assures accurate results from patients as well as professionals.

One-button operation, easy-to-see display and film-strip accuracy make the GLUCOMETER 3 System so simple, it's hard to go wrong. We know, because we didn't limit our studies to experienced evaluators. We also gathered precision and accuracy data from patients with diabetes who tested themselves. Patients of various ages and types of diabetes. As charts A and B show, this means GLUCOMETER 3 System accuracy and simplicity are right for patients, right for professionals.

## Fact: Precision variability is 4% or less.

A laboratory study using the GLUCOMETER 3 System yielded the precision data shown here. Good precision assures more reliable blood glucose results.




## Fact: GLUCOFILM Test Strips provide the widest hematocrit range available for blood glucose levels from 20-500 mg/dL.

Hematocrit levels from 20% to 60% have shown no significant effect on blood glucose results.

## Fact: The GLUCOMETER 3 Diabetes Care System is affordable.

Try the GLUCOMETER 3 System and be your own judge of the facts behind this reliable, easy-to-use **and** affordable blood glucose monitoring system. Contact your Miles Inc., Diagnostics Division representative or write us at the address below.

*Introducing*
**Glucometer® 3**
Diabetes Care System
With New Glucofilm™ Test Strips

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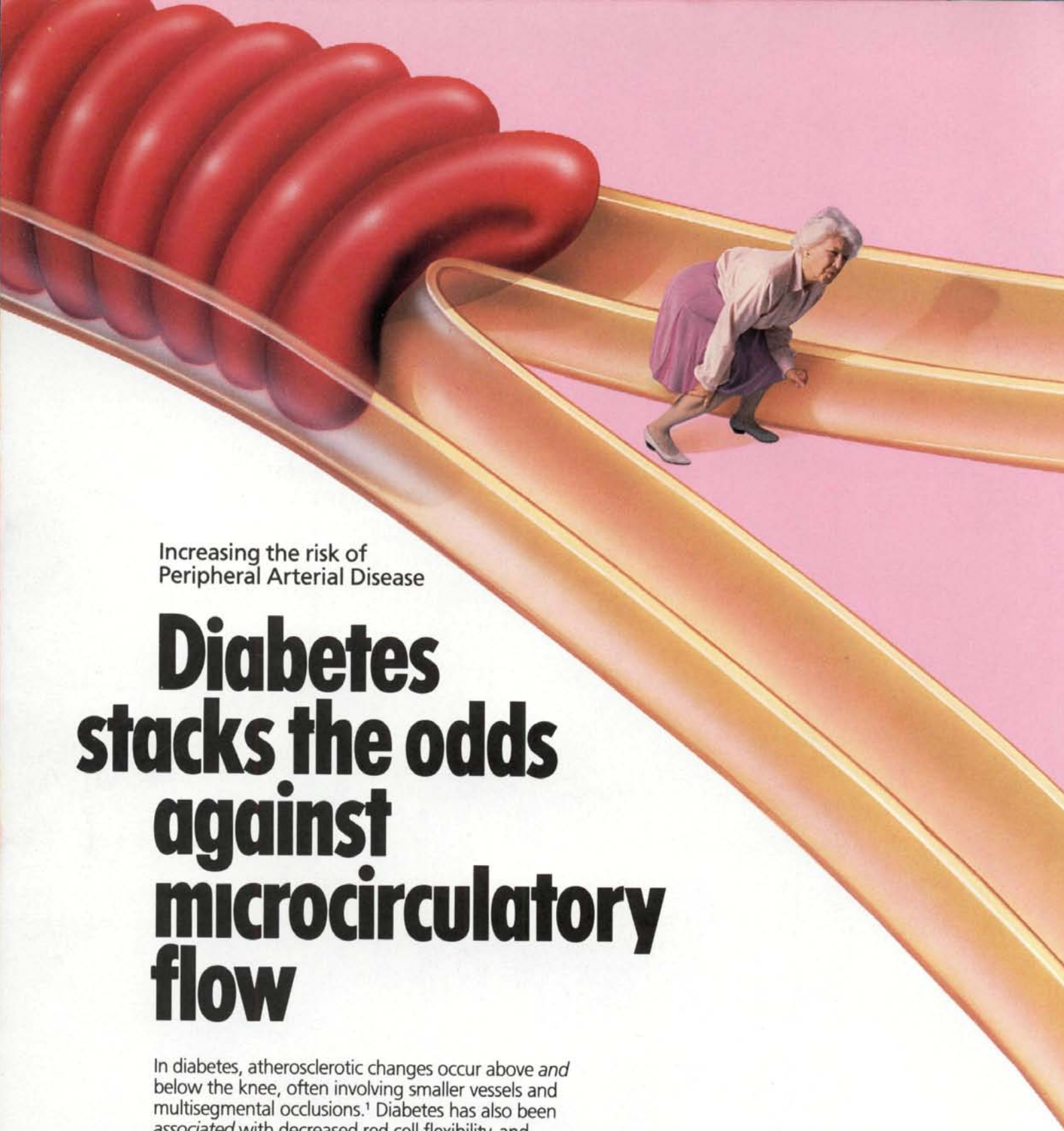
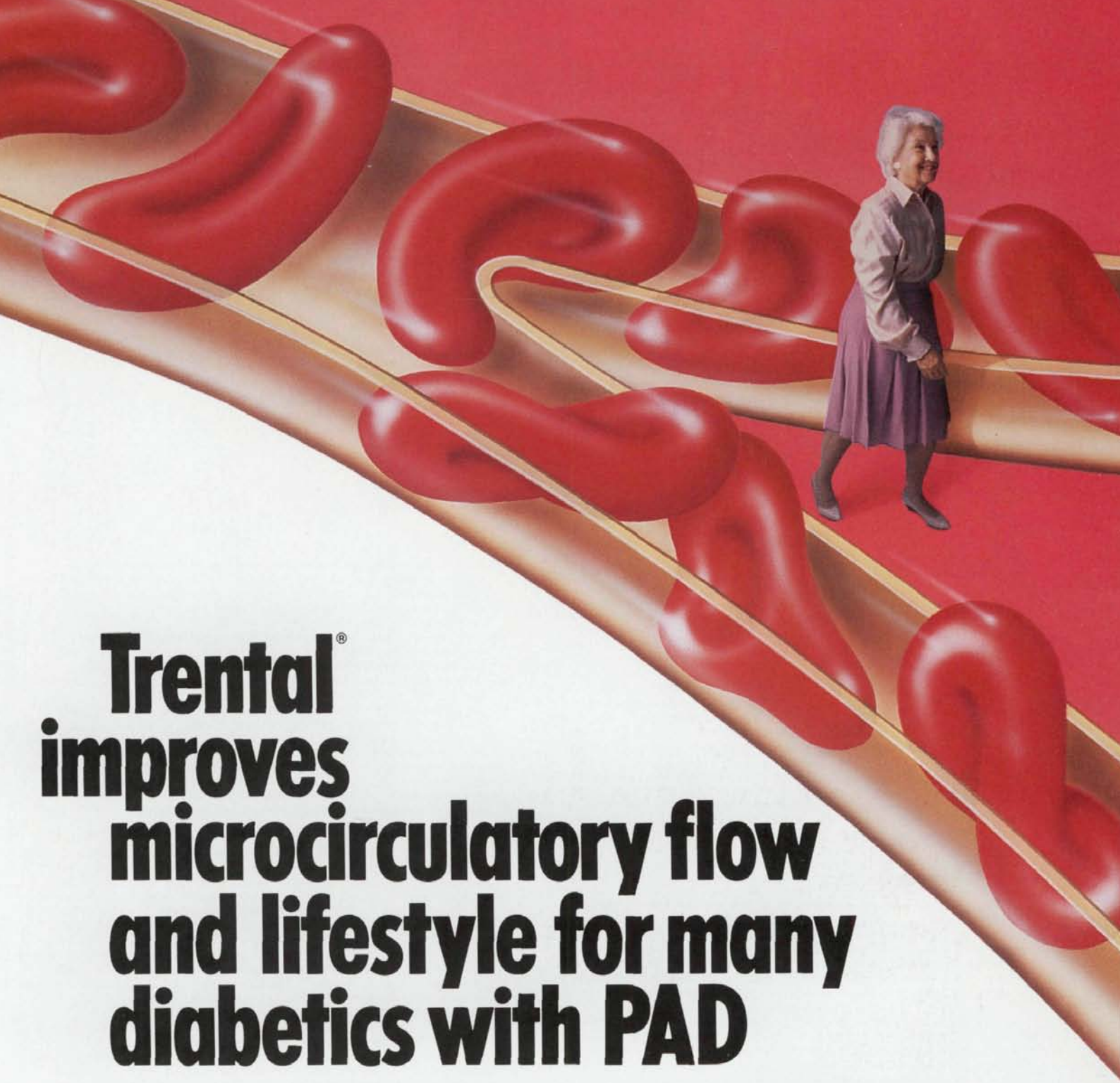


Increasing the risk of
Peripheral Arterial Disease

# Diabetes stacks the odds against microcirculatory flow

In diabetes, atherosclerotic changes occur above *and* below the knee, often involving smaller vessels and multisegmental occlusions.[1] Diabetes has also been *associated* with decreased red cell flexibility, and increasing fibrinogen levels, platelet aggregation and platelet adherence, factors which predispose patients to peripheral arterial disease.[1]

| Duration of Diabetes | Incidence of PAD |
|---|---|
| 10 years | 15% |
| 20 years | 45% |



# Trental® improves microcirculatory flow and lifestyle for many diabetics with PAD

Trental® (pentoxifylline) increases red cell flexibility[2] while decreasing elevated plasma fibrinogen levels,[3] aggregation of platelets[4] and red cells.[5] The resulting increase in microcirculatory flow enhances tissue perfusion and oxygenation.[6]

With Trental, patients experience significant improvement in pain-free walking distance, paresthesia, skin temperature and subjective overall response.[7]

**Not a vasodilator • Not an anticoagulant • Not related to aspirin or dipyridamole**

## Trental® 400 mg Tablets (pentoxifylline)

**The only proven-effective agent for intermittent claudication, a symptom of peripheral arterial disease**

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

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

**References:**
**1.** Levin ME, Sicard GA: Evaluating and treating diabetic peripheral vascular disease, Part I. *Clinical Diabetes* May/Jun 1987. **2.** Stormer B, Kleinschmidt K, Loose D, et al: Rheological changes in the blood of patients with chronic arterial occlusive disease after the administration of vasoactive drugs. *Curr Med Res Opin* 1977;4:588-595. **3.** Perego MA, Sergio G, Artale F: Haemorrheological aspects of the pathophysiology and clinical features of peripheral occlusive arterial disease. *Pharmatherapeutica* 1983;3(1):91. **4.** Seiffge D: *IRCS Med Sci* 1980;8:727. **5.** Lowe GDO, Drummond MM, Forbes CD, et al: Blood and plasma viscosity in prediction of venous thrombosis. Abstracts: 77, International Symposium on Filterability and Red Blood Cell Deformability, Göteborg, Sweden, Sep 11-13, 1980. **6.** Ehrly AM: Effects of orally administered pentoxifylline on muscular oxygen pressure in patients with intermittent claudication. *IRCS Med Sci* 1982;10:401. **7.** Schubotz R: Double-blind trial of pentoxifylline in diabetes with peripheral vascular disorders. *Pharmatherapeutica* 1976;1(3):172-179.

**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 | |
|---|---|---|---|---|
| | Commercially Available | | Used only for Controlled Clinical Trials | |
| | 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, angioedema.
Special Senses—blurred vision, conjunctivitis, earache, scotoma.
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, increased liver enzymes; and Hemic and Lymphatic—decreased serum fibrinogen, pancytopenia, aplastic anemia, 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. Edition 2/88
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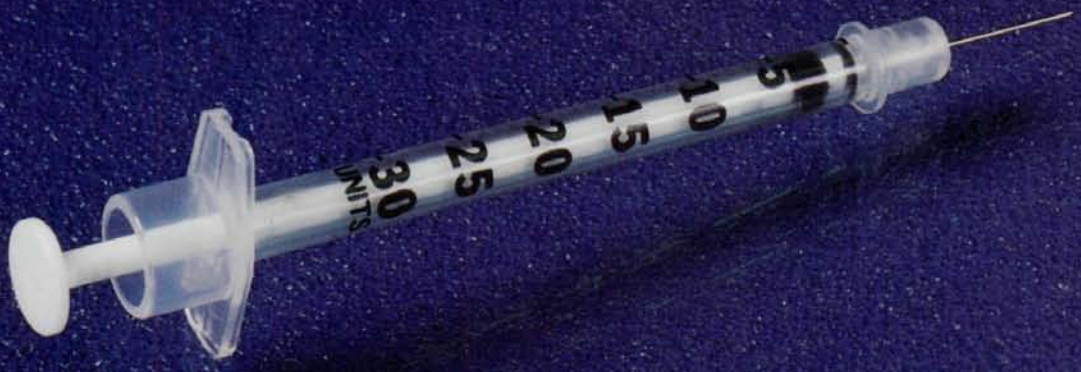


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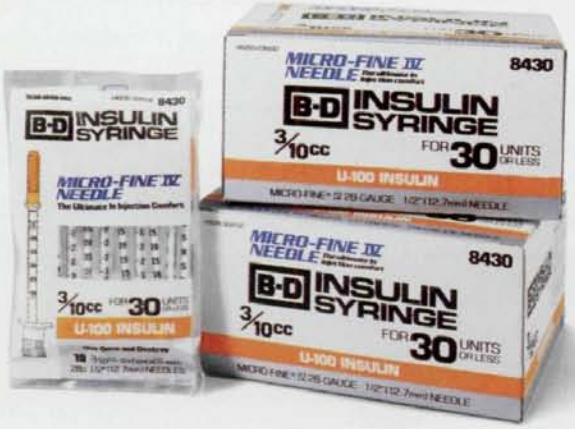


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# *We didn't get admitted to more hospitals by accident*


## *Accu-Chek® IIm Blood Glucose Monitor & Chemstrip bG® Test Strips*

## *Chosen by more hospitals for accuracy and precision[1]*

Accuracy and precision are only two reasons 7 out of 10 hospitals have selected the Accu-Chek® system for blood glucose monitoring of diabetic patients.[1] Today, this same hospital accuracy is available with the Accu-Chek® IIm Blood Glucose Monitor. Independent studies have proved that the Accu-Chek® IIm system outperforms every other major blood glucose monitor available.[1] Accuracy and precision studies show 100% acceptable results across the entire measured range of 20-500 mg/dL blood glucose.[1]

When used with Chemstrip bG® Test Strips, the Accu-Chek® IIm Blood Glucose Monitor provides the most accurate, precise system available. It is also the only blood glucose monitor that rejects most strips to which an inadequate amount of blood has been applied[2] and is the only monitor system cleared for use with neonates.[1] A 30-value memory lets patients record readings more conveniently.

Recommend the Accu-Chek® IIm Blood Glucose Monitor for *hospital accuracy* each time your patients test.

**References: 1.** Data on file, Boehringer Mannheim Diagnostics. **2.** Meters for glucose monitoring. *Med Lett Drugs Ther* 1988;30(778):101–102.

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ACS-169

# The burning, throbbing, lancinating pain of diabetic neuropathy...

Responds to

# NEW Axsain™

## capsaicin 0.075% cream

## C fiber specific analgesic for peripheral neuropathies

- Topical, with no known systemic effects or drug interactions; can easily be used adjunctively
- Unmyelinated C fiber selective; does not affect more discriminatory senses such as touch, pressure, or vibration

# Effective pain relief--improved comfort

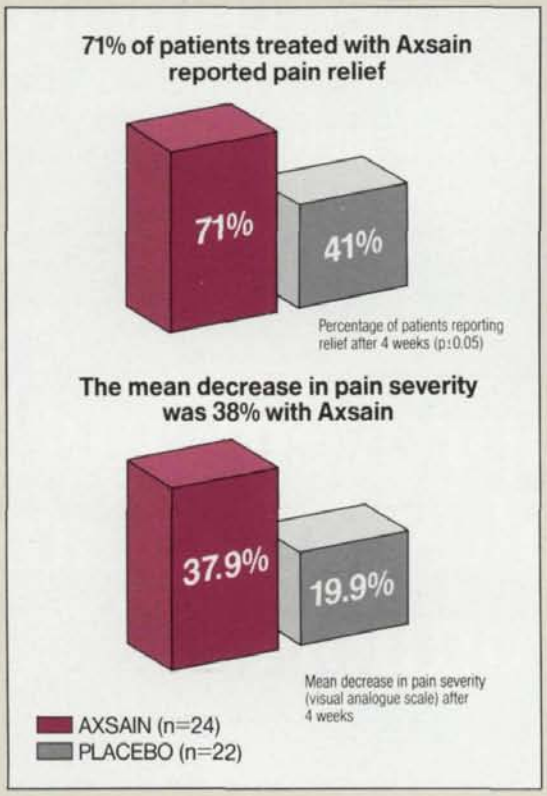
- Patients applying Axsain three to four times daily report noticeable pain relief within two to four weeks
- Side effects are few and minor

# Even moderate improvements in pain relief can make significant differences in comfort

Please see next page for brief summary of prescribing information

# NEW Axsain™
capsaicin 0.075% cream

## Effective analgesia demonstrated in double-blind, multi-center trial[1]




## Highly specific to cutaneous C fiber neurons

Capsaicin selectively depresses type C nociceptive fibers and causes a release and subsequent depletion of substance P, thereby impeding the conduction and transmission of peripheral pain impulses.

## Effective relief is achieved through proper patient use

For effective relief, Axsain must be applied to the affected area three to four times a day. Continued application is necessary for three to four weeks to realize optimal clinical response.

Axsain should be rubbed into the skin in amounts sufficient to cover the area without resulting in a caked residue.

A transient burning sensation and reddening of the skin may occur over the first several days of use. Application schedules less than three times a day may not provide optimal pain relief and may cause the burning sensation to persist.

Illustrated easy-to-read patient instruction booklets are included in every Axsain package.


NEW Axsain™ capsaicin 0.075% cream

**Description:** Axsain contains capsaicin 0.075% in an emollient cream base. Capsaicin is trans-8-methyl-N-vanillyl-6-nonenamide, a white crystalline powder with a molecular weight of 305.4. It is practically insoluble in water but very soluble in alcohol, ether and chloroform.

**Active Ingredient:** Capsaicin 0.075%.

**Inactive Ingredients:** Benzyl Alcohol, Cetyl Alcohol, Glyceryl Monostearate, Isopropyl Myristate, Polyoxyethylene Stearate Blend, Purified Water, Sorbitol Solution, White Petrolatum.

**Actions and Indications:** Current evidence suggests that Axsain works by its action on a pain transmitting compound called substance P. The capsaicin in Axsain causes substance P to leave the nerve endings. With a lower amount of substance P in the nerve endings, pain impulses cannot be transmitted to the brain. Axsain is indicated for relief of neuralgias (pain from nerves near the surface of the skin) such as painful diabetic neuropathy and postsurgical pain.

**Warnings:** Avoid contact with eyes. Do not apply to wounds or damaged skin. Do not bandage tightly. If condition worsens or does not improve after 28 days, discontinue use of this product and consult your physician. Keep this and all drugs out of the reach of children.

**Directions:** Adults and children 2 years of age and older: Apply to affected area 3 to 4 times daily. A transient burning sensation related to the action of the product may occur over the first several days of use. Application schedules less than 3 times a day may not provide optimum pain relief and the burning sensation may persist. Wash hands immediately after application avoiding areas where drug is applied.

**How Supplied:** 2.0 oz. tubes (NDC 57284-501-60) 005 0489
U.S. Patent Nos. 4,486,450 and 4,536,404 126344

1. Data on file 1989, GalenPharma, Inc.

GalenPharma™
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New Directions in The Management of Pain



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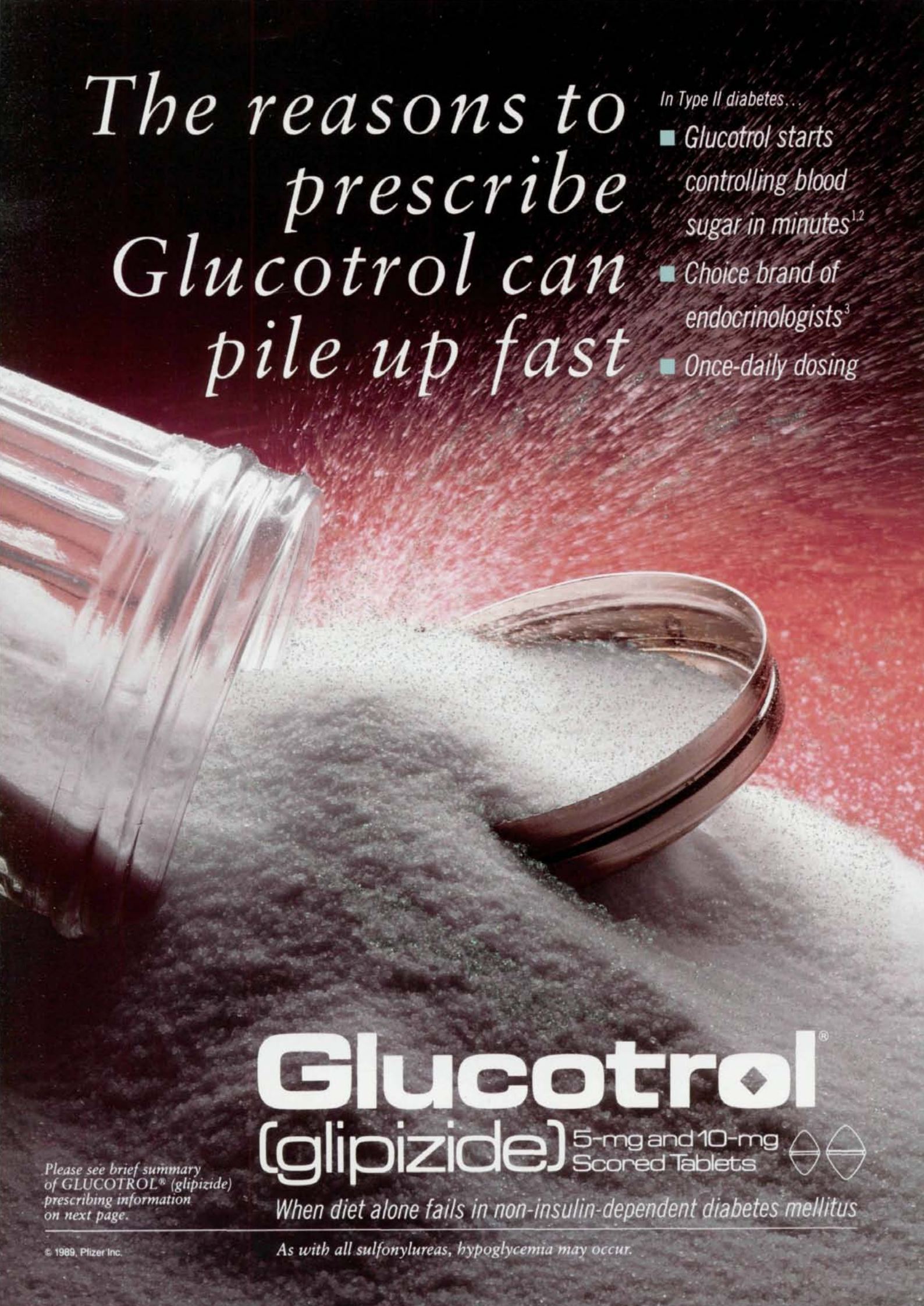
The reasons to prescribe Glucotrol can pile up fast
In Type II diabetes...
Glucotrol starts controlling blood sugar in minutes[1,2]
Choice brand of endocrinologists[3]
Once-daily dosing
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(glipizide) 5-mg and 10-mg Scored Tablets
When diet alone fails in non-insulin-dependent diabetes mellitus
Please see brief summary of GLUCOTROL® (glipizide) prescribing information on next page.
As with all sulfonylureas, hypoglycemia may occur.
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**References:** 1. Goebel R, Leb G: Effects of glyburide and glipizide on levels of immunoreactive insulin and blood sugar, in *Glipizide: A Worldwide Review*. Princeton, NJ, Excerpta Medica, 1984, pp 9-15. 2. Melander A, Wåhlin-Boll E: Clinical pharmacology of glipizide. *Am J Med* 1983;75:8-14.

**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 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. *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. A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known.

**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.

**Endocrine Reactions:** Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with this and other sulfonylureas.

**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, 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.

**CAUTION:** Federal law prohibits dispensing without prescription.

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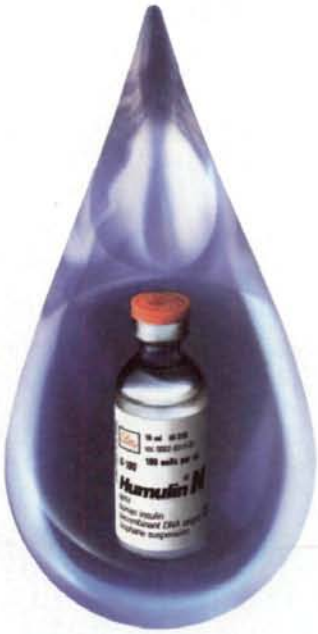


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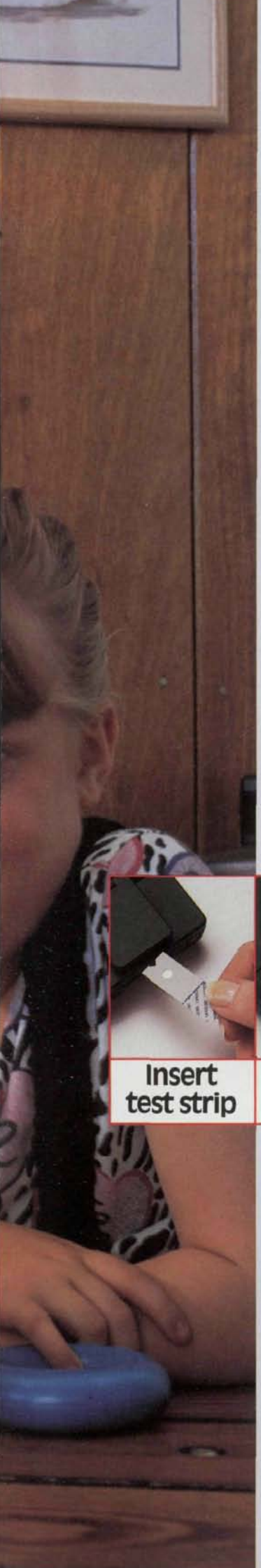

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1. Jovanovic-Peterson L., Peterson C., Dudley J., Kilo C., Ellis B.: Identifying sources of error in self-monitoring of blood glucose. Diabetes Care 1988; 11 (10) 791-794.

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[1] Roland JM: Need Stable Diabetics Mix Their Insulins? *Diabetic Medicine* 1985;2:51-53. 