

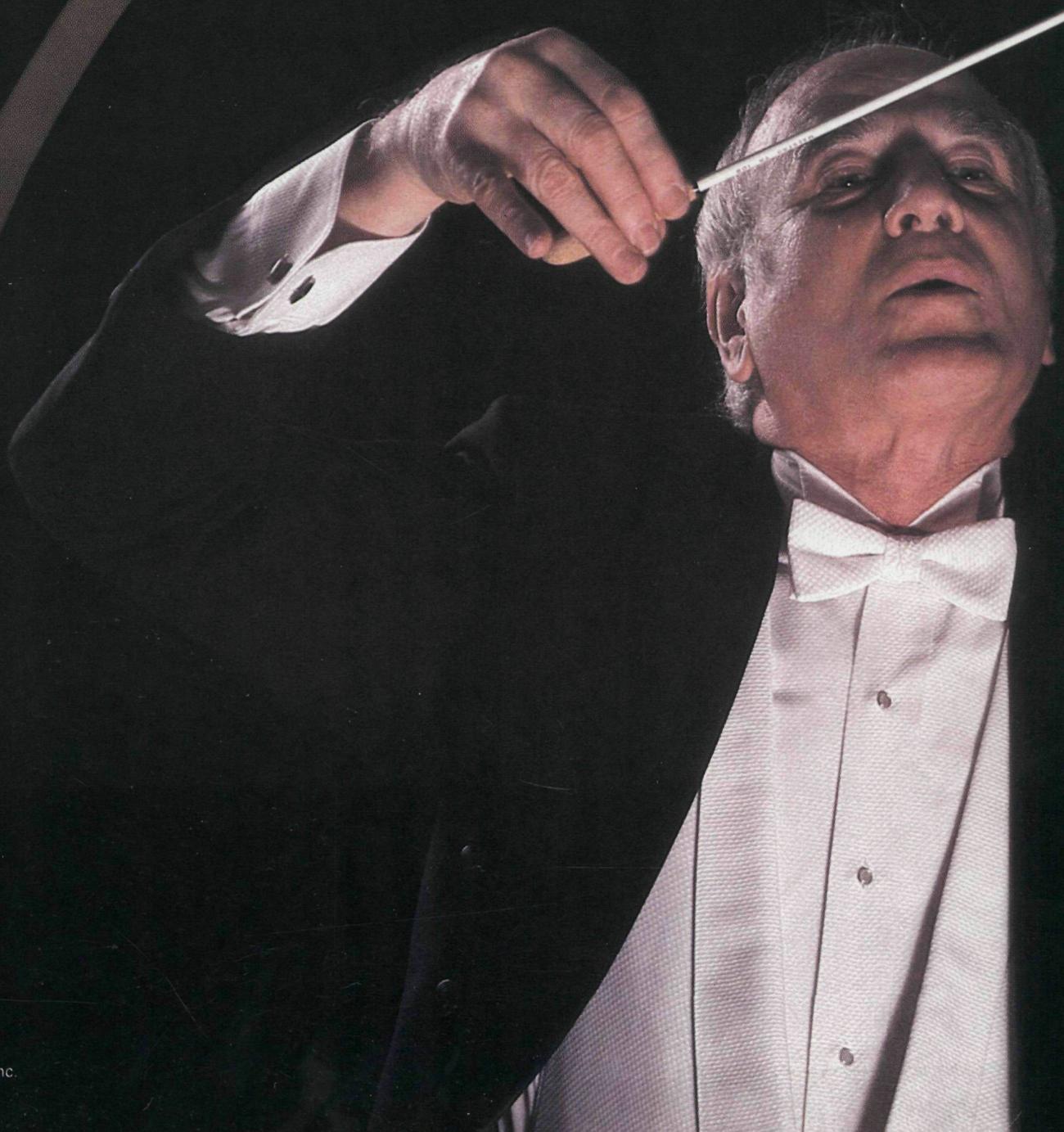
# diabetes

A JOURNAL OF  
THE AMERICAN  
DIABETES  
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<b>PRESIDENT'S ADDRESS</b>	1449
<b>ORIGINAL ARTICLES</b>	
Exogenous arachidonic acid promotes insulin release from intact or permeabilized rat islets by dual mechanisms: putative activation of Ca <sup>2+</sup> mobilization and protein kinase C S.A. METZ	1453
Metabolic effects of low-dose insulin therapy on glucose metabolism in diabetic ketoacidosis L. LUZI, E.J. BARRETT, L.C. GROOP, E. FERRANNINI, AND R.A. DeFRONZO	1470
Influence of cAMP and calcium on [ <sup>3</sup> H]inositol efflux, inositol phosphate accumulation, and insulin release from isolated rat islets W.S. ZAWALICH, V.A. DIAZ, AND K.C. ZAWALICH	1478
Alterations in T-lymphocyte subpopulations in type I diabetes: exploration of genetic influence in identical twins C. JOHNSTON, L. ALVIGGI, B.A. MILLWARD, R.D.G. LESLIE, D.A. PYKE, AND D. VERGANI	1484
Choline turnover in phosphatidylcholine of pancreatic islets: implications for CDP-choline pathway J.M. HOFFMAN AND S.G. LAYCHOCK	1489
Effect of proteinuria on mortality in NIDDM R.G. NELSON, D.J. PETTITT, M.J. CARRAHER, H.R. BAIRD, AND W.C. KNOWLER	1499
Prevention of sugar-induced cataractogenesis in rats by butylated hydroxytoluene S.K. SRIVASTAVA AND N.H. ANSARI	1505
Biosynthetic regulation of endogenous hamster insulin and exogenous rat insulin II in transfected HIT cells G. GOLD, M.D. WALKER, D.L. EDWARDS, AND G.M. GRODSKY	1509
Clarification of signaling pathways mediated by insulin and insulin-like growth factor I receptors in fibroblasts from patients with specific defect in insulin receptor T. SASAOKA, M. KOBAYASHI, Y. TAKATA, O. ISHIBASHI, M. IWASAKI, Y. SHIGETA, K. GOJI, AND A. HISATOMI	1515
Control of glucose metabolism in pancreatic $\beta$ -cells by glucokinase, hexokinase, and phosphofructokinase: model study with cell lines derived from $\beta$ -cells T. SHIMIZU, J.C. PARKER, H. NAJAFI, AND F.M. MATSCHINSKY	1524
Stimulation of glucose production through hormone secretion and other mechanisms during insulin-induced hypoglycemia R.T. FRIZZELL, G.K. HENDRICK, L.L. BROWN, D.B. LACY, E.P. DONAHUE, R.K. CARR, P.E. WILLIAMS, A.F. PARLOW, R.W. STEVENSON, AND A.D. CHERRINGTON	1531
Effect of <i>myo</i> -inositol and T <sub>3</sub> on myocardial lipids and cardiac function in streptozocin-induced diabetic rats H. XIANG, C.E. HEYLIGER, AND J.H. McNEILL	1542
Characterization of new oral antidiabetic agent CS-045: studies in <i>KK</i> and <i>ob/ob</i> mice and Zucker fatty rats T. FUJIWARA, S. YOSHIOKA, T. YOSHIOKA, I. USHIYAMA, AND H. HORIKOSHI	1549
Relationship of hepatic glucose uptake to intrahepatic glucose concentration in fasted rats after glucose load C.B. NIEWOEHNER AND F.Q. NUTTALL	1559
Effect of fish oil concentrate on lipoprotein composition in NIDDM G. SCHECTMAN, S. KAUL, AND A.H. KISSEBAH	1567
Cyclosporin-induced remission of IDDM after early intervention: association of 1 yr of cyclosporin treatment with enhanced insulin secretion THE CANADIAN-EUROPEAN RANDOMIZED CONTROL TRIAL GROUP	1574
<b>RAPID PUBLICATIONS</b>	
Regulation of glucose-transporter gene expression by insulin in cultured human fibroblasts A. KOSAKI, H. KUZUYA, Y. YOSHIMASA, K. YAMADA, M. OKAMOTO, H. NISHIMURA, T. KAKEHI, J. TAKEDA, Y. SEINO, AND H. IMURA	1583
Autoantibodies in nonobese diabetic mice immunoprecipitate 64,000-M, islet antigen M.A. ATKINSON AND N.K. MACLAREN	1587
<b>ORGANIZATION SECTION</b>	



# TIMING IS KEY



# EVERYTHING

## Effective control time and time again<sup>1</sup>

Effective control of fasting and postprandial glucose—patient after patient, meal after meal, year after year.

## Insulin when it's needed

Insulin levels are rapidly elevated in response to a meal, then return promptly to basal levels after the meal challenge subsides.

## Timed to minimize risks

Rapidly metabolized and excreted, with an excellent safety profile.<sup>1</sup> As with all sulfonylureas, hypoglycemia may occur.

In concert with diet in non-insulin-dependent diabetes mellitus

**Glucotrol<sup>®</sup>**  
(glipizide) 5-mg and 10-mg  
Scored Tablets



**SYNCHRONIZED  
SULFONYLUREA THERAPY**



*Please see brief summary of Glucotrol<sup>®</sup> (glipizide) prescribing information on next page.*

**ROERIG**   
A division of Pfizer Pharmaceuticals  
New York, New York 10017

**Reference:**

1. Sachs R, Frank M, Fishman SK: Overview of clinical experience with glipizide. In *Glipizide: A Worldwide Review* Princeton, NJ, Excerpta Medica, 1984, pp 163-172.

**GLUCOTROL® (glipizide) Tablets**

**Brief Summary of Prescribing Information**

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

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

**SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY:** The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes*, 19, supp. 2:747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of GLUCOTROL and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

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

**Hypoglycemia:** All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemia. Renal or hepatic insufficiency may increase the risk of hypoglycemic reactions. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly or people taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

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

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

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

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

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

**DOSE 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 0049-4120-65) Bottles of 100.

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

More detailed professional information available on request.

NOVEMBER AUTHOR INDEX

(Volume 37, Number 11)

Alvigi, L., 1484	Maclaren, N.K., 1587
Ansari, N.H., 1505	Matschinsky, F.M., 1524
Atkinson, M.A., 1587	McNeill, J.H., 1542
	Metz, S.A., 1453
Baird, H.R., 1499	Millward, B.A., 1484
Barrett, E.J., 1470	
Brown, L.L., 1531	Najafi, H., 1524
	Nelson, R.G., 1499
Carr, R.K., 1531	Niewoehner, C.B., 1559
Carraher, M.J., 1499	Nishimura, H., 1583
Cherrington, A.D., 1531	Nuttall, F.Q., 1559
Colwell, J.A., 1449	
	Okamoto, M., 1583
DeFronzo, R.A., 1470	
Diaz, V.A., 1478	
Donahue, E.P., 1531	Parker, J.C., 1524
	Parlow, A.F., 1531
Edwards, D.L., 1509	Pettitt, D.J., 1499
	Pyke, D.A., 1484
Ferrannini, E., 1470	
Frizzell, R.T., 1531	Sasaoka, T., 1515
Fujiwara, T., 1549	Schectman, G., 1567
	Seino, Y., 1583
Goji, K., 1515	Shigeta, Y., 1515
Gold, G., 1509	Shimizu, T., 1524
Grodsky, G.M., 1509	Srivastava, S.K., 1505
Groop, L.C., 1470	Stevenson, R.W., 1531
Hendrick, G.K., 1531	Takata, Y., 1515
Heyliger, C.E., 1542	Takeda, J., 1583
Hisatomi, A., 1515	The Canadian-European
Hoffman, J.M., 1489	Randomized Control
Horikoshi, H., 1549	Trial Group, 1574
Imura, H., 1583	Ushiyama, I., 1549
Ishibashi, O., 1515	
Iwasaki, M., 1515	Vergani, D., 1484
Johnston, C., 1484	Walker, M.D., 1509
	Williams, P.E., 1531
Takehi, T., 1583	
Kaul, S., 1567	Xiang, H., 1542
Kissebah, A.H., 1567	
Knowler, W.C., 1499	Yamada, K., 1583
Kobayashi, M., 1515	Yoshimasa, Y., 1583
Kosaki, A., 1583	Yoshioka, S., 1549
Kuzuya, H., 1583	Yoshioka, T., 1549
Lacy, D.B., 1531	Zawalich, K.C., 1478
Laychock, S.G., 1489	Zawalich, W.S., 1478
Leslie, R.D.G., 1484	
Luzi, L., 1470	

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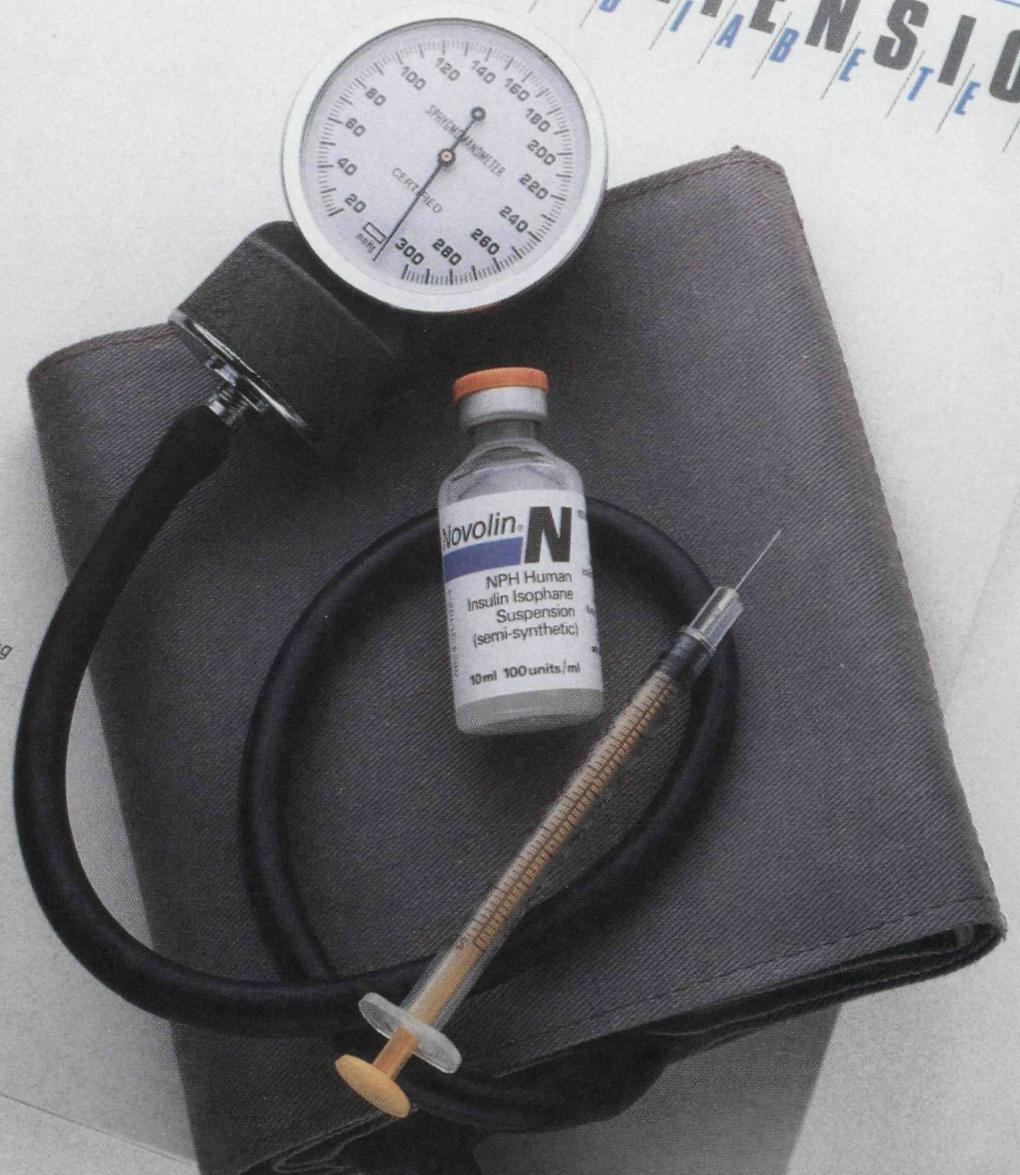
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**FINAL REPORT**

The Working Group on Hypertension in Diabetes:

**CAPOTEN<sup>®</sup>** (captopril tablets)  
**FIRST-LINE THERAPY**  
**FOR HYPERTENSIVE DIABETIC**  
**PATIENTS\***

**HYPERTENSION**  
**IN** **DIABETES**



Final Report of the Working  
Group on Hypertension  
in Diabetes

Approved by the  
National High Blood Pressure  
Education Program  
Coordinating Committee on  
January 16, 1987

**A** National High Blood Pressure  
Education Program

## *Controls hypertension today*

CAPOTEN controls blood pressure without altering insulin secretion or complicating diabetes management.<sup>1,2</sup>

## *Offers potential long-term benefits*

CAPOTEN does not deplete potassium or alter lipid levels.

# THE CAPOTEN<sup>®</sup> (captopril tablets) DIFFERENCE



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

References:

1. The Working Group on Hypertension in Diabetes: Statement on Hypertension in Diabetes Mellitus: Final Report. Arch Intern Med 147:830-842, 1987.
2. D'Angelo A, Sartori L, Gambaro G, et al: Captopril in the treatment of hypertension in type I and type II diabetic patients. Postgrad Med J 62(suppl 1):69-72, 1986.

# THE CAPOTEN<sup>®</sup> (captopril tablets) DIFFERENCE

## CAPOTEN<sup>®</sup> 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.

**CONTRAINDICATIONS:** CAPOTEN is contraindicated in patients who are hypersensitive to this product.

**WARNINGS: Neutropenia/Agranulocytosis**—Neutropenia ( $<1000/\text{mm}^3$ ) 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 less than 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 the subsequent clinical experience. Of reported cases, about half had serum creatinine  $\geq 1.6$  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 white cell 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  $<1000/\text{mm}^3$ ) withdraw captopril and closely follow the patient's course.

**Proteinuria:** Total urinary proteins  $>1$  g per 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 with captopril, patients with prior renal disease or those receiving captopril at doses  $>150$  mg per 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 the 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 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 of 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. Embryonic 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. CAPOTEN (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 has 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 has been 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**—Approximately 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, 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 hypertension 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).

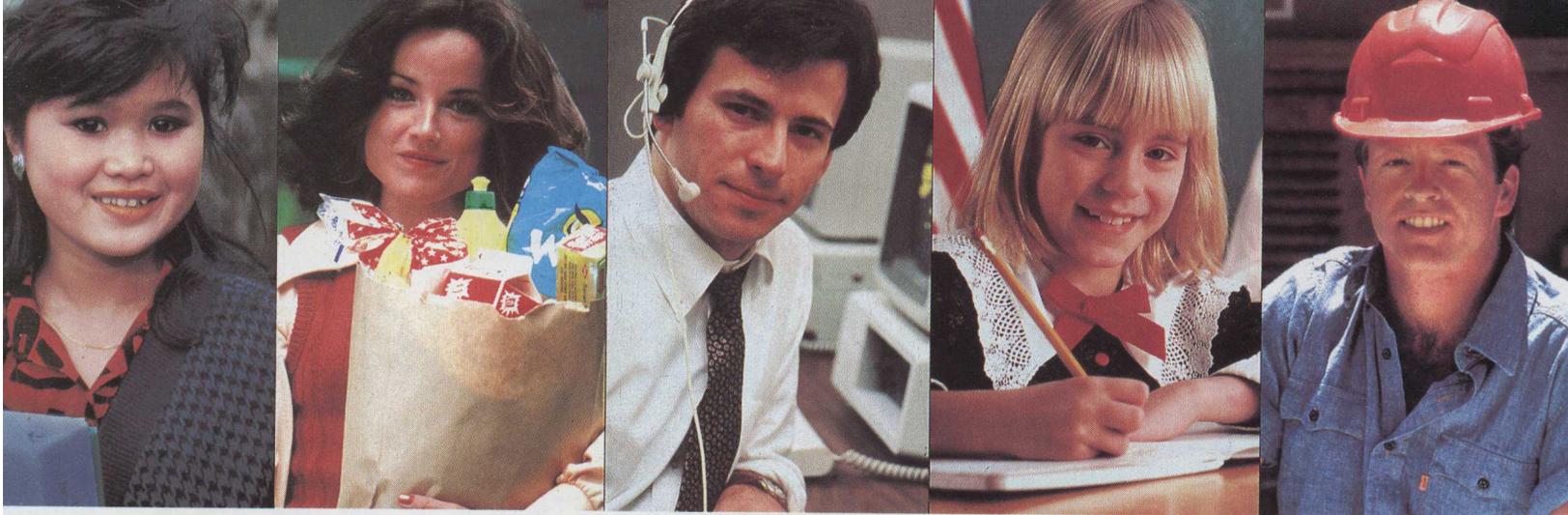
**OVERDOSAGE:** Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

**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, and 50 mg in bottles of 100 and 1000; 100 mg in bottles of 100; and in UNIMATIC<sup>®</sup> unit-dose packs of 100 tablets. (J3-658K)





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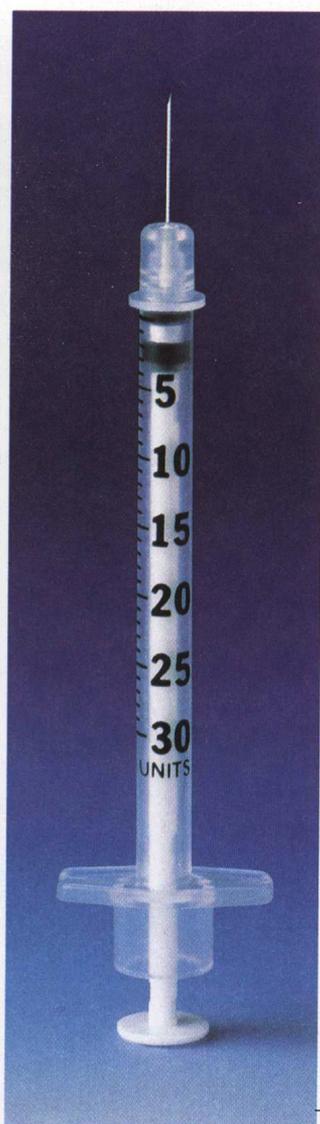
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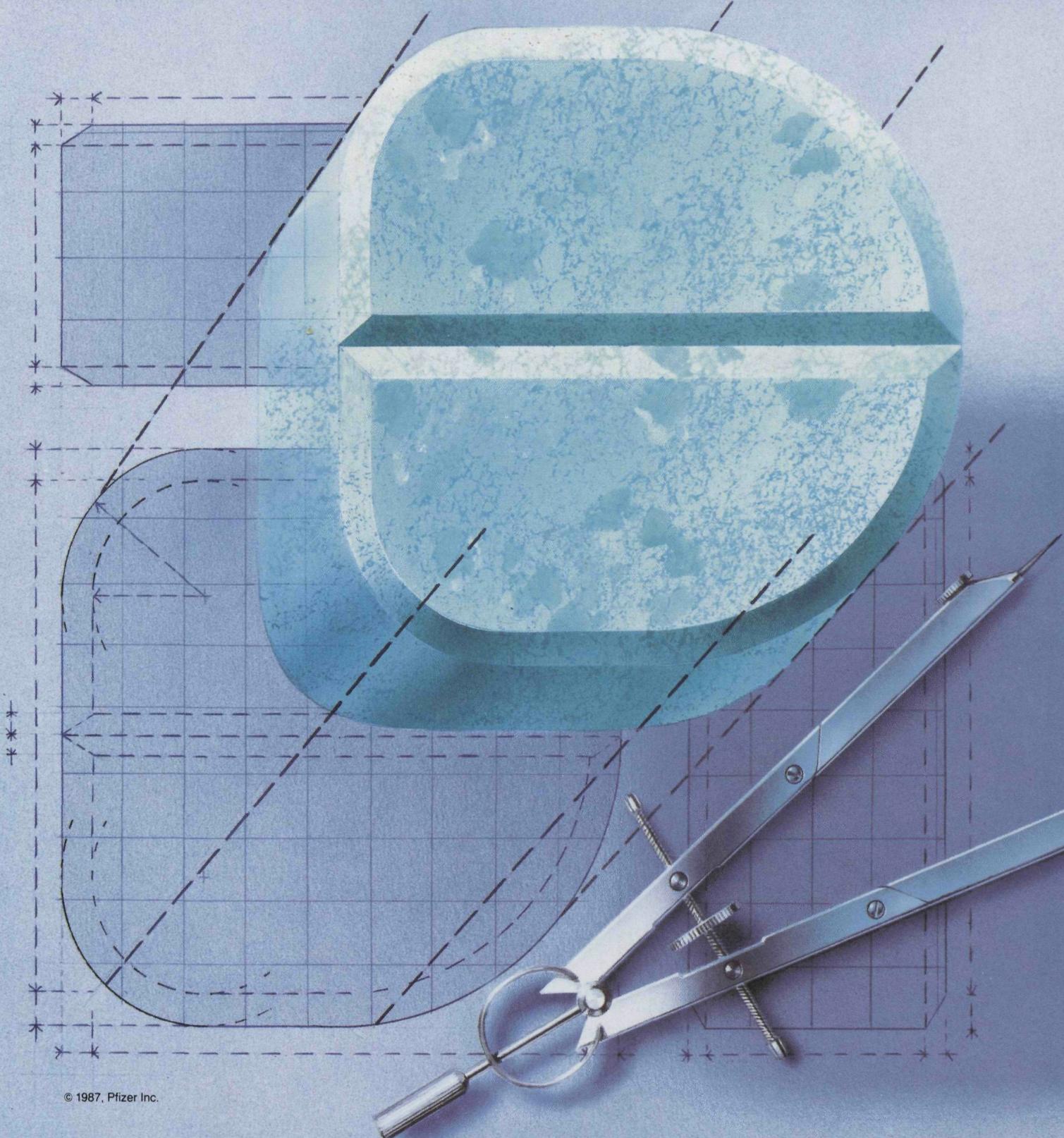
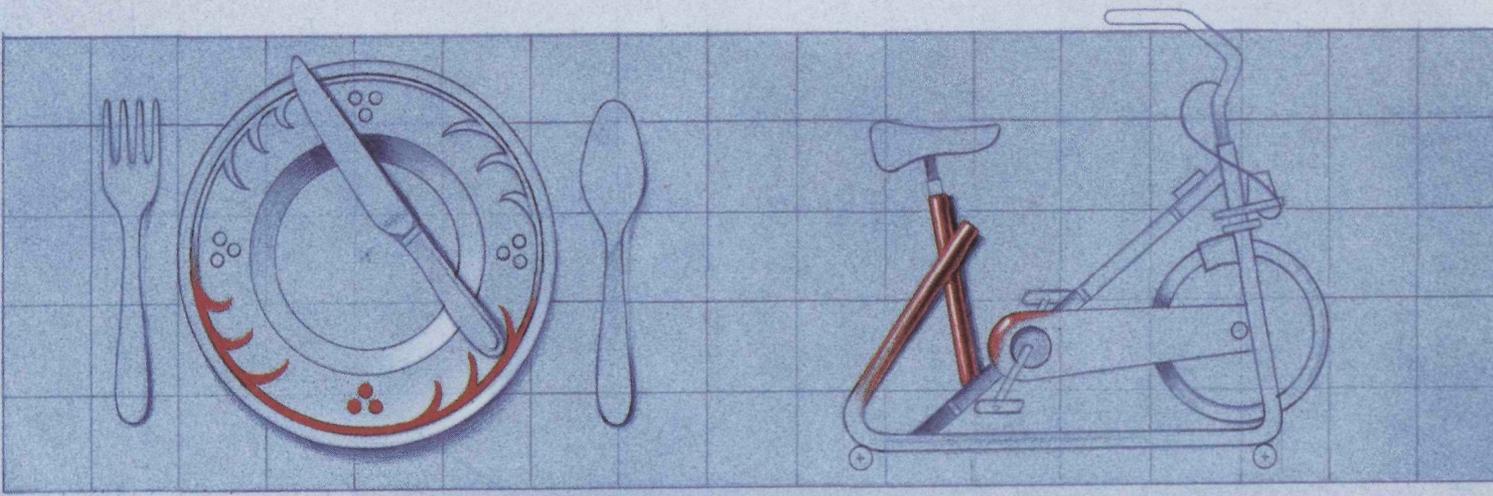


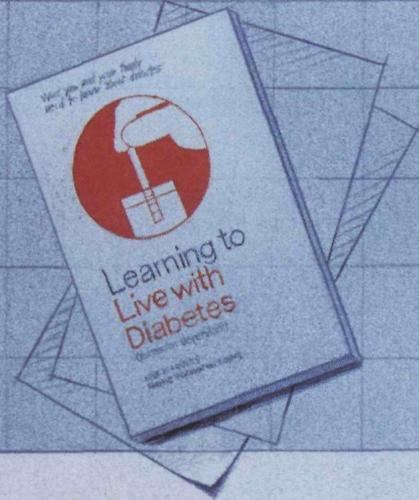
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In a two-year study comparing Diabinese® to glyburide, "...chlorpropamide was clinically more effective with a smaller number of primary and secondary drug failures and a greater proportion of patients successfully controlled at the end of 2 years. Severe hypoglycemia was a greater hazard during treatment with glyburide...."<sup>1</sup>

As with all sulfonylureas, hypoglycemia may occur with Diabinese.

Once-a-day

# Diabinese®

(chlorpropamide) Tablets, USP, 100 mg, 250 mg and D-Pak

A GENERATION AHEAD IN NIDDM CONTROL

Reference: 1. Clarke BF: Comparative effectiveness of glyburide in the treatment of non-insulin-dependent diabetes, in *Diagnosis and Management of Diabetes Mellitus*. Postgraduate Medicine: Custom Communications, April 1982, pp 57-65.

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

**Pfizer** LABORATORIES DIVISION  
PFIZER INC. NEW YORK, N.Y. 10017



BRIEF SUMMARY  
**DIABINESE**® (chlorpropamide)  
 TABLETS, USP

**CONTRAINDICATIONS**

- DIABINESE is contraindicated in patients with:
1. Known hypersensitivity to the drug.
  2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

**WARNINGS**

**SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY**

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes*, 19 [supp. 2]:747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of DIABINESE (chlorpropamide) and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

**PRECAUTIONS**

**General**

**Hypoglycemia:** All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may cause elevated blood levels of DIABINESE and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Because of the long half-life of chlorpropamide, patients who become hypoglycemic during therapy require careful supervision of the dose and frequent feedings for at least 3 to 5 days. Hospitalization and intravenous glucose may be necessary.

**Loss of control of blood glucose:** When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue DIABINESE (chlorpropamide) and administer insulin.

The effectiveness of any oral hypoglycemic drug, including DIABINESE, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given.

**ADVERSE REACTIONS**

**Hypoglycemia:** See PRECAUTIONS section.

**Gastrointestinal Reactions:** Cholestatic jaundice may occur rarely. DIABINESE should be discontinued if this occurs. Gastrointestinal disturbances are the most common reactions; nausea has been reported in less than 5% of patients, and diarrhea, vomiting, anorexia, and hunger in less than 2%. Other gastrointestinal disturbances have occurred in less than 1% of patients including proctocolitis. They tend to be dose related and may disappear when dosage is reduced.

**Dermatologic Reactions:** Pruritus has been reported in less than 3% of patients. Other allergic skin reactions, e.g., urticaria and maculopapular eruptions have been reported in approximately 1% or less of patients. These may be transient and may disappear despite continued use of DIABINESE (chlorpropamide); if skin reactions persist the drug should be discontinued.

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

Skin eruptions rarely progressing to erythema multiforme and exfoliative dermatitis have also been reported.

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

**Metabolic Reactions:** Hepatic porphyria and disulfiram-like reactions have been reported with DIABINESE.

**Endocrine Reactions:** On rare occasions, chlorpropamide has caused a reaction identical to the syndrome of inappropriate antidiuretic hormone (ADH) secretion. The features of this syndrome result from excessive water retention and include hyponatremia, low serum osmolality, and high urine osmolality.

**DOSEAGE AND ADMINISTRATION**

There is no fixed dosage regimen for the management of diabetes mellitus with DIABINESE or any other hypoglycemic agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, and to detect secondary failure. Glycosylated hemoglobin levels may also be of value in monitoring the patient's response to therapy.

The total daily dosage is generally taken at a single time each morning with breakfast. Occasionally cases of gastrointestinal intolerance may be relieved by dividing the daily dosage. A LOADING OR PRIMING DOSE IS NOT NECESSARY AND SHOULD NOT BE USED.

**Initial Therapy:** 1. The mild to moderately severe, middle-aged, stable, non-insulin-dependent diabetic patient should be started on 250 mg daily. Older patients should be started on smaller amounts of DIABINESE (chlorpropamide), in the range of 100 to 125 mg daily.

2. No transition period is necessary when transferring patients from other oral hypoglycemic agents to DIABINESE. The other agent may be discontinued abruptly and chlorpropamide started at once. In prescribing chlorpropamide, due consideration must be given to its greater potency.

Many mild to moderately severe, middle-aged, stable non-insulin-dependent diabetic patients receiving insulin can be placed directly on the oral drug and their insulin abruptly discontinued. For patients requiring more than 40 units of insulin daily, therapy with DIABINESE may be initiated with a 50 per cent reduction in insulin for the first few days, with subsequent further reductions dependent upon the response.

Five to seven days after the initial therapy, the blood level of chlorpropamide reaches a plateau. Dosage may subsequently be adjusted upward or downward by increments of not more than 50 to 125 mg at intervals of 3 to 5 days to obtain optimal control. More frequent adjustments are usually undesirable.

**Maintenance Therapy:** Most moderately severe, middle-aged, stable non-insulin-dependent diabetic patients are controlled by approximately 250 mg daily. Many investigators have found that some milder diabetics do well on daily doses of 100 mg or less. Many of the more severe diabetics may require 500 mg daily for adequate control. PATIENTS WHO DO NOT RESPOND COMPLETELY TO 500 MG DAILY WILL USUALLY NOT RESPOND TO HIGHER DOSES. MAINTENANCE DOSES ABOVE 750 MG DAILY SHOULD BE AVOIDED.

**HOW SUPPLIED**

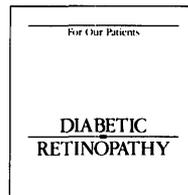
Blue, 'D'-shaped, scored tablets in strengths of 100 mg, tablet code 393; (100's, NDC #0663-3930-66; 500's, NDC #0663-3930-73; and 100 unit dose of 10 X 10, NDC #0663-3930-41) and 250 mg, tablet code 394; (100's, NDC #0663-3940-66; 250's, NDC #0663-3940-71; 1000's, NDC #0663-3940-82; 100 unit dose of 10 X 10, NDC #0663-3940-41; and 30's D-Pak, NDC #0663-3940-30).

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

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

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## ERRATA

The May issue of *Diabetes* contains an error in the article "Glomerular Na<sup>+</sup>-K<sup>+</sup>-ATPase Activity in Acute and Chronic Diabetes and With Aldose Reductase Inhibition," by Margo P. Cohen and Henry Klepser. The last sentence of the first paragraph of DISCUSSION (p. 560) should read "A report of increased Na<sup>+</sup>-K<sup>+</sup>-ATPase activity in renal cortex from STZ-D rats used animals with diabetes of 4-7 wk duration, and the increase was ascribed to the tubular Na<sup>+</sup> pump activity (17)."

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In the August issue, in the last sentence of the figure legend on p. 1126, the words *top* and *bottom* were reversed. The editors at the publishing office apologize for the error.

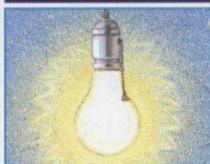
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1660 Duke Street  
Alexandria, VA 22314  
or telephone 1-800-ADA-DISC.

# INNOVATIONS IN TECHNOLOGY FOR OPTIMAL DIABETES MANAGEMENT



**Accu-Chek® II<sub>m</sub>**  
Blood Glucose Monitor

**MERLIN™**  
DIABETES DATA  
MANAGEMENT SYSTEM

*THE LINE OF CONFIDENCE<sup>SM</sup>  
IN DIABETES CONTROL*

## NEW ACCU-CHEK® II<sub>m</sub> BLOOD GLUCOSE MONITOR FOR ADDED TESTING CONVENIENCE

The ACCU-CHEK® II<sub>m</sub> Monitor offers your patients two important features for greater convenience: a 30-value memory for storing blood glucose values and a beeper privacy switch for "silent" testing when desired. In the same tradition of excellence as the currently available ACCU-CHEK® II model, you can be assured of accurate results.<sup>1</sup> Furthermore, ACCU-CHEK® II<sub>m</sub> uses CHEMSTRIP bG® Test Strips — the preferred blood glucose strip.<sup>2</sup> Both ACCU-CHEK® II and II<sub>m</sub> are ideal for use with the MERLIN™ Diabetes Data Management System.



## NEW MERLIN™ DIABETES DATA MANAGEMENT SYSTEM FOR BETTER PATIENT LIFESTYLE MANAGEMENT

The MERLIN™ System goes far beyond data storage and traditional data management by allowing you to evaluate diabetes control to accomplish better patient lifestyle management. Key to the convenience of the system is the Electronic Log Book (ELB) with a 250-record memory. In addition, the MERLIN™ System features a unique software program for use with a personal computer or printer.

For improving diabetes control, the ACCU-CHEK® II m Monitor and the MERLIN™ System are unbeatable... combining advanced technology with the added convenience of memory.

*For more information, please call toll-free 1-800-858-8072.*

References: 1. Data on file, Boehringer Mannheim Diagnostics. 2. Nielsen Audits (Jan.-Feb., 1988).

**BOEHRINGER  
MANNHEIM  
DIAGNOSTICS**

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**First hundreds...**



**Then thousands...**

**Soon more than a million.**

**Soon more than a million insulin users will be taking Humulin.**

And no wonder. Humulin is identical to the insulin produced by the human pancreas—except that it is made by rDNA technology.

Humulin is not derived from animal pancreases. So it contains none of the animal-source pancreatic impurities that may contribute to insulin allergies or immunogenicity.

The clinical significance of insulin antibodies in the complications of diabetes is uncertain at this time. However, high antibody titers have been shown to decrease the small amounts of endogenous insulin secretion some insulin users still have. The lower immunogenicity of Humulin has been shown to result in lower insulin antibody titers; thus, Humulin may help to prolong endogenous insulin production in some patients.

**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), species/source (beef, pork, beef-pork, or human), and/or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage.

**DIET...EXERCISE...**

**Humulin**®   
human insulin  
(recombinant DNA origin)

**For your insulin-using patients**

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**Lilly Leadership**  
IN DIABETES CARE



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