Membership in the Professional Section of the American Diabetes Association,® Inc.

The Professional Section of the American Diabetes Association is open to physicians, research scientists and all other health care professionals who have a particular interest in the study and treatment of diabetes mellitus.

Membership provides: 1) educational opportunities through research symposia and postgraduate courses scheduled throughout the year (C.M.E. credit for attendance at ADA sponsored meetings is available from the American Medical Association, the American Academy of Family Physicians, the American Dietetic Association and State Nursing Associations); 2) membership in Councils, which are a valuable forum for discussing new findings and information with colleagues in specific areas of diabetes research and care; 3) an opportunity to participate in program and policy development through service on ADA committees and appointment to the ADA Board of Directors.

Membership benefits include:

- Reduced registration fees for ADA postgraduate and scientific sessions.
- Eligibility for ADA research grants and awards for major contributions in diabetes research. (see next page)
- Membership in one Council. (Dues for each additional Council are $20.00 annually.)
- Membership in your local ADA Affiliate.
- The receipt of the Annual Directory of Professional Members.
- The receipt of DIABETES (with supplements)*, the monthly publication for physicians and those in other scientific fields concerned with diabetes and related endocrine and metabolic disorders, which contains major scientific papers and review articles, reviews, rapid publications, editorials and Association news.
- The receipt of DIABETES CARE (with supplements), the unique bi-monthly for health care professionals aimed at improving the care of patients with diabetes through the presentation of research advances with clinical relevance, timely reviews of diabetic complications and their management, and the policies of the ADA on control, diagnosis, diet, and therapy.
- The receipt of CLINICAL DIABETES, the bi-monthly newsletter for the primary-care physician that highlights, in a clear, jargon-free style, current scientific information and clinical findings about diabetes as they apply to the care of the patient.
- The receipt of DIABETES FORECAST, the bi-monthly consumer publication written for the person with diabetes and their family, which provides the latest research developments and up-to-date information on the causes, treatment, and care of diabetes and aims to help its readers achieve a better understanding and acceptance of diabetes.
- The receipt of DIABETES '84, the quarterly newsletter for people who live with diabetes, aimed at providing basic information about diabetes care including articles on diet, medication, exercise, self-testing, insulin and the most recent research advances.

* M.D. professionals receive DIABETES as part of their membership. Other health care professionals have the option of receiving all membership perquisites except DIABETES.

ADA Scientific Grants and Awards

Feasibility Grants
are given to assist investigators who want to test the feasibility of diabetes-related new and imaginative ideas in order to obtain preliminary data upon which a subsequent research grant application could be based. These grants provide financial support and are available to scientists affiliated with institutions within the United States and U.S. possessions.

Research and Development Awards
are given to assist exceptionally promising investigators in the transition to the level of established investigator. This award provides financial support for scientists within the United States and U.S. possessions.

For grant applications, please contact the Assistant Coordinator of Research at the American Diabetes Association.

The Lilly Award
is given annually to acknowledge the importance of independence of thought and originality in diabetes research; to identify those research scientists who have excelled in this area; to reward the most outstanding efforts in diabetes research; and to stimulate excellence among research scientists in diabetes research.

The Ames Award
is given annually to acknowledge the importance of teaching efforts in the field of diabetes; to identify those health professionals who have excelled in this area; to reward the most outstanding efforts in the field of diabetes education; and to stimulate others to initiate, participate, and excel in the area of diabetes education.

The Pfizer Award
is given annually to acknowledge the importance of excellence of care by clinicians in the management of diabetes mellitus; to stimulate the identification of individuals who have achieved excellence in the field; to reward the most outstanding efforts in patient care; and to stimulate excellence among professionals in the field.

The Upjohn Award
is given annually to acknowledge the importance of teaching efforts in the field of diabetes; to identify physicians who have excelled in this area; to reward the most outstanding efforts in the field of diabetes education; and to stimulate others to initiate, participate, and excel in the area of diabetes education.

Membership
in the Professional Section is for twelve months. Annual membership dues are $125.00 for M.D. professionals. Other health care professionals have the option of paying $125.00 or $65.00. Those paying $65.00 DO NOT receive the Journal DIABETES.

Professional Membership
entitles you to become a member of one Council and dues for each additional Council membership are $20.00 annually. Council membership coincides with the twelve-month period of Professional Membership.

Annual dues
for qualified individuals who have received their first professional degree, diploma, or certificate during the preceeding five years are one-half the regular amount. Such members are designated "Student Members".

Members
of the Professional Section in good standing may, upon request, become Emeritus Members, having all the privileges of membership without the payment of dues, provided they have attained the age of 65, have retired, and have had continuous membership in the Association for 20 years.

If members wish to receive back issues of publications, they may order them separately, subject to availability.

Please complete
both sides of the application form on the opposite page, detach and return with your dues payment to the American Diabetes Association, attention: Professional Membership Coordinator. If you desire membership in more than one Council, please also include $20.00 for each additional Council membership.

We look forward to receiving you as a member and to your participation in the activities of the American Diabetes Association.

American Diabetes Association®

Professional Membership Section
2 Park Avenue, New York, New York 10016,1-800-227-6776

Application for Professional Section

FOR OFFICE USE ONLY
Date of admission _____ Amount paid $_____
PM code _____ Specialty code _____
Student _____ Through _____
Mail to: ___ office ___ res.
Air Mail ___ First Class ___

Please print as it should appear on mailing label:

Name _____
(Last Name) (First Name) (Middle Initial) (Degree)

Office _____
Street City State Zip Code Office Telephone Number (include area code)

Residence _____
Street City State Zip Code Residence Telephone Number (include area code)

Date of Birth *_____
Please mail my Journals to my: ☐ Office ☐ Residence
Please send my Journals by: ☐ Air Mail ☐ First Class
(billed separately)

Qualifications for Professional Section

Education

_____ 19 _____ to 19 _____ Degree _____
College

_____ 19 _____ to 19 _____ Degree _____
University

_____ 19 _____ to 19 _____ Degree _____
Medical School

_____ 19 _____ to 19 _____
Internship (Hospital-Service)

_____ 19 _____ to 19 _____
Residencies (Hospital-Service)

Hospital Affiliations and Appointments

_____ _____

_____ _____

Medical School Appointments

_____ _____

_____ _____

*Information is required to determine eligibility for emeritus status.

(over)

Councils of the Professional Section

Council on Diabetes in Pregnancy
This Council provides a forum for persons interested in treatment, pathophysiology of metabolic abnormalities, basic understanding of fetal development, nutrition, and other areas related to diabetes in pregnancy.

Council on Diabetes in Youth
The specific aim of this Council is to provide pediatricians and pediatric-related professionals with a forum for the exchange of information on education and research as it relates to children and adolescents.

Council on Epidemiology and Statistics
Emphasizing the epidemiology of diabetes, its complications, and their impact on national health care needs and policy, this Council aims to promote the exchange of information and to further scientific knowledge and research in this area.

Council on Nutrition
This Council is designed for those interested in nutrition and aims to stimulate research and discussion and provide an expert "voice" on nutritional issues.

Council on Public Health Care Delivery
This Council provides information on current issues relating to the delivery of health care to people with diabetes and examines issues in third-party reimbursement, guidelines for primary-care practitioners and standards for patient education and management.

Please check one:

☐ As a M.D. professional or as a health care professional (non-M.D.), I enclose $125.00 as payment for my annual membership dues.

☐ As a health care professional, I enclose $65.00 as payment for my annual membership dues.

Please check the one Council you wish to join as a benefit of Professional Membership. Also, check any additional Councils you wish to join and enclose $20.00 for each additional Council membership.

☐ Council on Diabetes in Pregnancy
☐ Council on Diabetes in Youth
☐ Council on Epidemiology and Statistics
☐ Council on Nutrition
☐ Council on Public Health Care Delivery

If Appropriate, check below:

☐ As a STUDENT M.D. professional or health care professional (non-M.D.), I enclose $62.00 as payment for my annual membership dues.

☐ As a STUDENT health care professional, I enclose $32.00 as payment for my annual membership dues.

☐ I am enclosing $_____ for membership in ____ additional Council(s). (#)

The following information is needed for the ADA's Annual Directory of Professional Members. Please check one of the following specialties for your Directory listing:

☐ Administration	(AD)	☐ Education	(ED)	☐ Neurology	(NR)	☐ Pharmacology	(PA)
☐ Anatomy	(AN)	☐ Epidemiology	(EP)	☐ Nursing	(NS)	☐ Podiatry	(PO)
☐ Anesthesiology	(AE)	☐ Endocrinology	(EN)	☐ Nutrition	(NU)	☐ Psychiatry	(PS)
☐ Biology	(BI)	☐ General Practice	(GP)	☐ Obstetrics/ Gynecology	(OG)	☐ Psychology	(PC)
☐ Biochemistry	(BC)	☐ Geriatrics	(GE)			☐ Public Health	(PH)
☐ Cardiology	(CA)	☐ Internal Medicine	(IM)	☐ Ophthalmology	(OP)	☐ Research	(RE)
☐ Dentistry	(DO)	☐ Immunology	(IU)	☐ Orthopedics	(OR)	☐ Surgery	(SU)
☐ Dermatology	(DE)	☐ Metabolism	(ME)	☐ Pediatrics	(PE)	☐ Urology	(UR)
☐ Diabetes	(DM)	☐ Nephrology	(NE)				

Signed _____ Dated _____

Please allow 3-4 weeks for processing of application.
All foreign payments must be prepaid in U.S. funds drawn on a U.S. bank.

Artist's interpretation of Glucotrol (glipizide) theoretical effects on the membrane barrier of hepatic cells, rendering them responsive to insulin, which unblocks the transmembrane transport of glucose.

Please see last page for Glucotrol® (glipizide) prescribing information.

Breaking barriers to glucose control in NIDDM: Glucotrol® (glipizide)

AMELIORATES METABOLIC DEFECTS

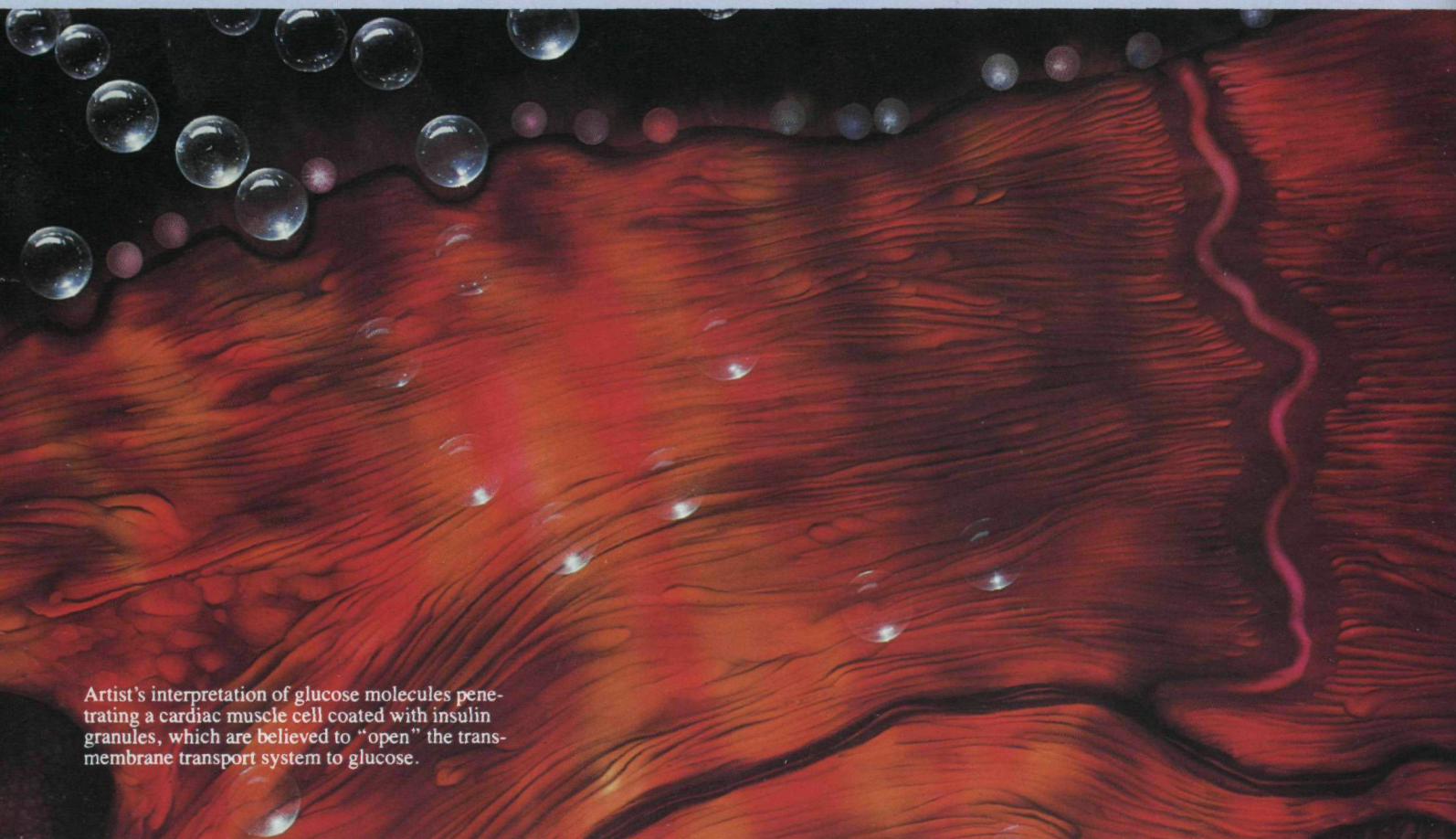
Inadequate secretion of insulin by pancreatic beta cells and impaired insulin action at target cells appear to be basic pathophysiologic abnormalities in NIDDM.[1-3] Although the mechanism of action is still under investigation, it appears that Glucotrol may exert its antidiabetic effect not only by increasing nutrient-stimulated insulin secretion (pancreatic) but also by potentiating insulin action (extrapancreatic).

The pancreatic effect: Glucotrol acts at the beta cell to stimulate insulin secretion

Glucotrol appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas in response to a meal. Fasting insulin levels are not elevated even on long-term Glucotrol administration, but the postprandial insulin response continues to be enhanced after at least six months of treatment.

Extrapancreatic effects:

There is also increasing evidence that extra-pancreatic effects involving potentiation of insulin action form a significant component of the activity of Glucotrol. Studies have demonstrated that the antidiabetic effects of Glucotrol may be related to this potentiation which leads to improvement of glucose utilization.[4-6]

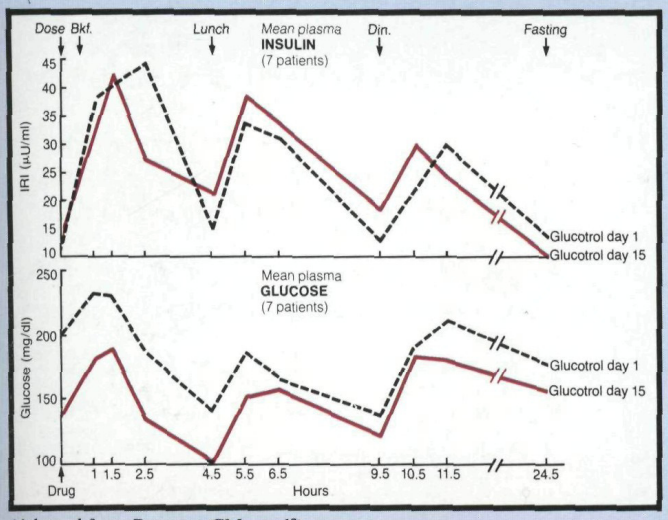


Artist's interpretation of glucose molecules penetrating a cardiac muscle cell coated with insulin granules, which are believed to "open" the transmembrane transport system to glucose.

SIMULATES THE PHYSIOLOGIC PATTERN OF INSULIN RESPONSE TO GLUCOSE CHALLENGE[8]

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

☐ Graphically, the insulin response pattern with Glucotrol closely simulates the pattern commonly seen in nondiabetics.

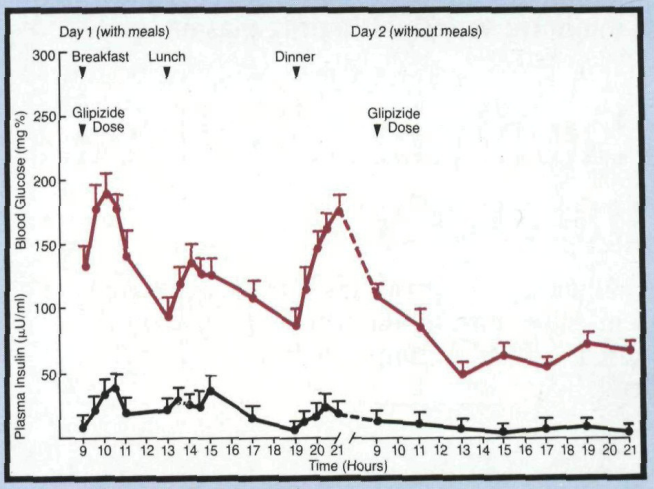


(Adapted from Peterson CM, et al[7])

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

Elevated insulin levels do not persist between meals[8]

No increased insulin secretion in the fasting state[8]



(Adapted from Clarke BF, et al[8])

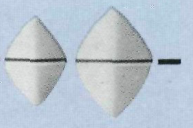
Mean values of blood glucose in mg/100 ml and I.R.I. in μU/ml plotted against time for six diabetics treated with a single morning dose of Glucotrol (glipizide), 5 to 10 mg, with standard diet on day one and no meals on day two. Even on day two, no hypoglycemic reactions were reported by any of these patients.[8] (In routine clinical use Glucotrol should be administered with or before a meal.) As with all sulfonylureas, hypoglycemia may occur with Glucotrol.

New

When diet alone fails in NIDDM

Glucotrol®

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



ROERIG Pfizer

Please see last page for Glucotrol® (glipizide) prescribing information.

Breaking barriers to glucose control in NIDDM: Glucotrol® (glipizide)

DISTINCTIVE PHARMACOKINETIC PROFILE

Rapid and essentially complete absorption[7]

☐ Rapid absorption and uniform bioavailability to minimize variations in drug plasma levels.

Rapidly metabolized... and excreted[9]

☐ Glucotrol (glipizide) is rapidly converted to inactive metabolites which are quickly excreted,[9] thus limiting accumulation of active drug.

Short plasma half-life– long duration of action[7]

☐ Blood sugar control persists in some patients up to 24 hours after a single dose of Glucotrol, even though plasma concentrations declined to a small fraction of peak levels.

Artist's interpretation of insulin granules being released from capsular sacs of a pancreatic beta-cell, disintegrating in extracellular space and passing through capillary wall.

DEMONSTRATED EFFICACY

Glucose control documented in clinical studies

In a series of controlled clinical trials, Glucotrol was evaluated in 360 non-insulin-dependent diabetics, the majority of whom had been failures on diet alone or with other oral agents.[10]

☐ Effective reduction of blood sugar (mean reduction was 31%) among 240 patients who came under control with Glucotrol therapy.

☐ Effective control in 78% of 85 patients previously treated with diet therapy alone.

☐ Effective control in 50% of 131 patients failing on other oral agents.

Criteria for effective control were two consecutive values of fasting plasma glucose (FPG) below 180 mg%. In patients with a baseline below 180 mg% before therapy, a reduction of FPG greater than 10% from baseline had to be achieved to be considered effective control.

Long-term success rate[11] documented

Level of control* in 52 long-term responders during one to six years of Glucotrol (glipizide) therapy

Level of Response (FPG mg%)	No. of Patients	% of total Patients
Excellent (FPG≤130)	23	44%
Good (FPG 131-150)	11	21%
Fair (FPG 151-180)	13	25%
Poor (FPG>180)	5	10%

*Based on the mean of the last three FPG values. (Adapted from Stravinski S, Love SJ[11])

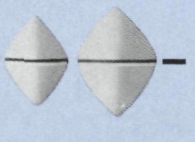
As with all sulfonylureas, primary and secondary failures may be seen with Glucotrol.

New

When diet alone fails in NIDDM®

Glucotrol

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



ROERIG Pfizer

Please see last page for Glucotrol® (glipizide) prescribing information.

Breaking barriers to glucose control in NIDDM: Glucotrol® (glipizide)

AN EXCELLENT SAFETY PROFILE

Well tolerated

In 702 patients treated with Glucotrol (glipizide) the most common reactions were:[10]

in slightly more than 2% of patients	in 1-2% of patients
dizziness (2.25%) lack of energy (2.13%)	drowsiness (1.75%) nausea (1.38%) headache (1.25%) sweating (1.25%) diarrhea (1.25%)

(Adapted from Sachs R, Frank M, Fishman SK[10])

☐ Only 1.5% of patients required discontinuance of therapy.

☐ Extremely low incidence of disulfiram-like reactions.

☐ As with all sulfonylureas, hypoglycemia may occur.

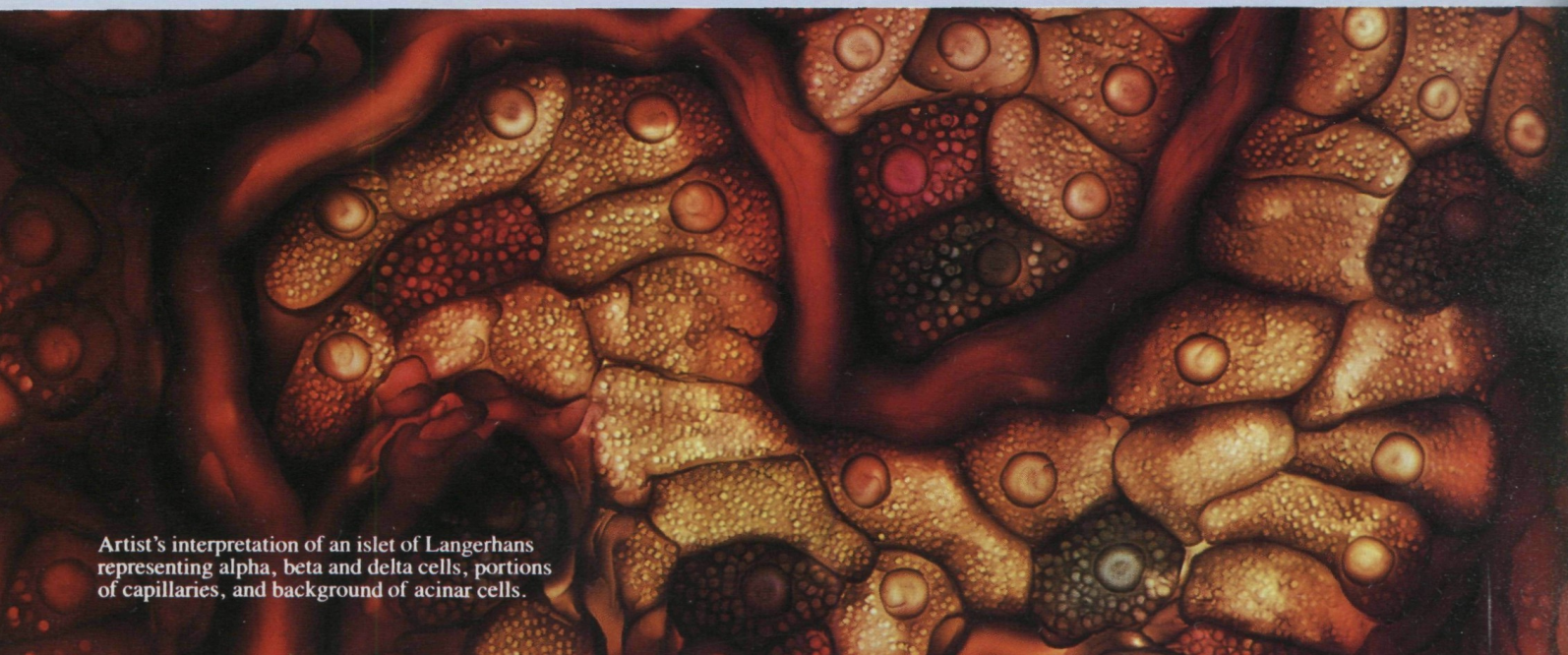
While controversy remains in the findings of UGDP, there have been reports of increased cardiovascular risk associated with oral hypoglycemic therapy.

No deleterious effects on lipid metabolism[12]

☐ It has been shown that Glucotrol therapy was effective in controlling blood sugar without deleterious changes in the plasma lipoprotein profiles of patients treated for NIDDM.

References:

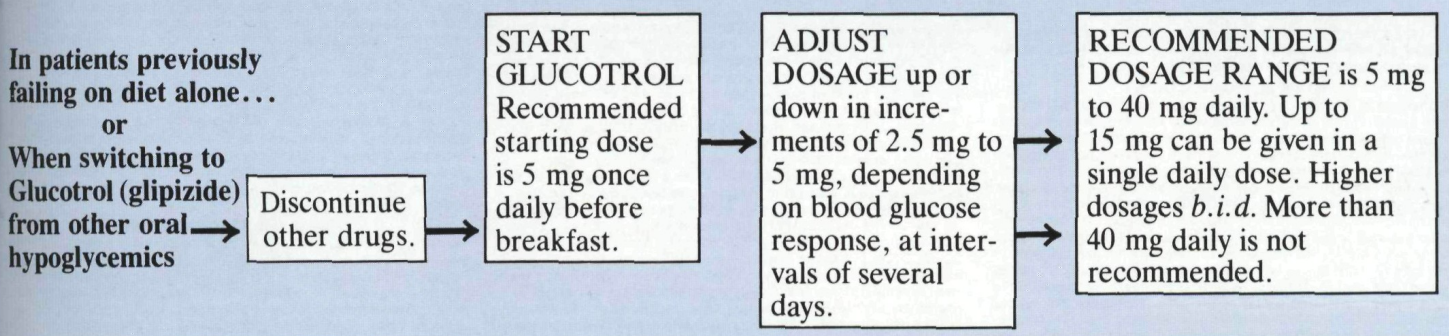
1. Reaven GM, Bernstein R, Davis B, et al: Nonketotic diabetes mellitus: Insulin deficiency or resistance? *Am J Med* 1976; 60:80-88. **2.** Defronzo R, Diebert D, Hendler R, et al: Direct evidence of insulin resistance in maturity-onset diabetes. *Diabetes* 1978; 27(Suppl 1): Abstract 4. **3.** Lohmann D, Ellorhaoui M, Verlohren HJ: Reduced insulin response in diabetes—A quantitative or a qualitative problem? *Horm Metab Res* 1977; 9:444-447. **4.** Feinglos MN, Lebovitz HE: Sulfonylurea treatment of insulin-independent diabetes mellitus. *Metabolism* 1980; 29:488-494. **5.** Reaven GM: Effect of glipizide treatment on various aspects of glucose, insulin, and lipid metabolism in patients with non-insulin-dependent diabetes mellitus, in *Proceedings of a Symposium: New Perspectives in Noninsulin-Dependent Diabetes Mellitus and the Role of Glipizide in Its Treatment. Am J Med*, pp. 8-14, Nov. 30, 1983. **6.** Lebovitz HE, Feinglos MN: Mechanism of action of the second-generation sulfonylurea glipizide, in *Proceedings of a Symposium: New Perspectives in Noninsulin-Dependent Diabetes Mellitus and the Role of Glipizide in Its Treatment. Am J Med*, pp. 46-54, Nov. 30, 1983. **7.** 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. **8.** Clarke BF, Corrall RJM, Azzopardi J, et al: Clinical observations on glipizide: Efficacy, duration of activity and safety. *First International Glipizide Symposium*. Princeton, NJ, Excerpta Medica, March 24-25, 1977 (to be published). **9.** Balant L, Fabre J: Pharmacokinetics of glipizide in man. *First International Glipizide Symposium*. Princeton, NJ, Excerpta Medica, March 24-25, 1977 (to be published). **10.** Sachs R, Frank M, Fishman SK (Pfizer Laboratories Division, Pfizer Inc.): Overview of clinical experience with glipizide. *First International Glipizide Symposium*. Princeton, NJ, Excerpta Medica, March 24-25, 1977 (to be published). **11.** Stravinski S, Love SJ (Pfizer Laboratories Division, Pfizer Inc.): Long-term experience with glipizide. *First International Glipizide Symposium*. Princeton, NJ, Excerpta Medica, March 24-25, 1977 (to be published). **12.** Greenfield MS, Doberne L, Rosenthal M, et al: Lipid metabolism in non-insulin-dependent diabetes mellitus: Effect of glipizide therapy. *Arch Intern Med* 1982; 142:1498-1500.

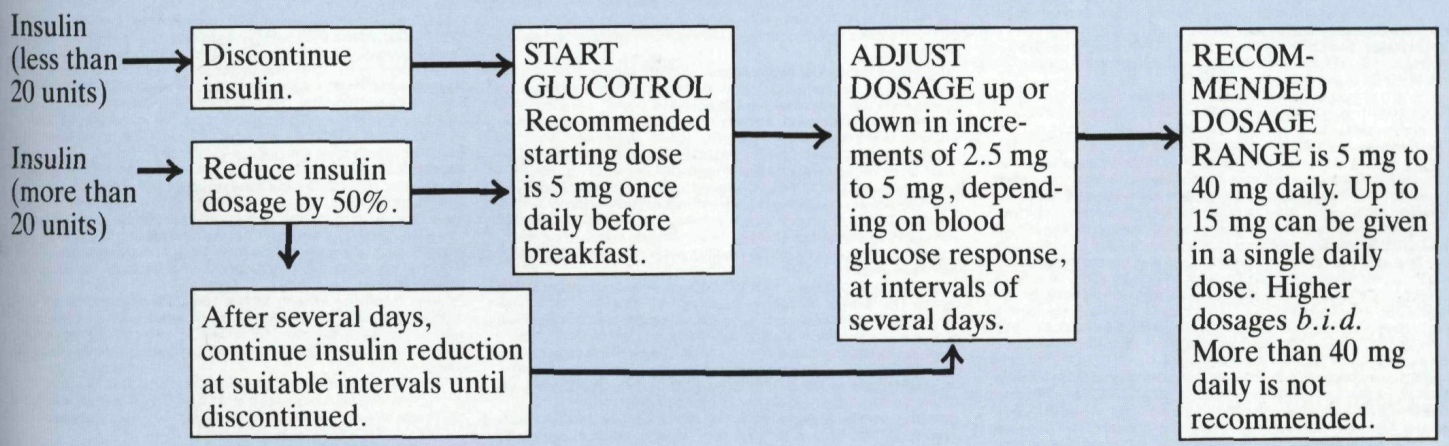


Artist's interpretation of an islet of Langerhans representing alpha, beta and delta cells, portions of capillaries, and background of acinar cells.

Convenient dosage regimen

Dosage Guide



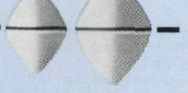


New

When diet alone fails in NIDDM

Glucotrol®

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



ROERIG Pfizer

Please see last page for Glucotrol® (glipizide) prescribing information.

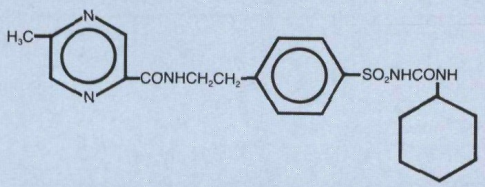
GLUCOTROL® (glipizide) TABLETS

For Oral Use

DESCRIPTION

GLUCOTROL (glipizide) is an oral blood-glucose-lowering drug of the sulfonylurea class.

The Chemical Abstracts name of glipizide is 1-cyclohexyl-3-[[p-[2-(5-methylpyrazinecarboxamido)ethyl]phenyl]sulfonyl]urea. The molecular formula is $C_{21}H_{27}N_5O_4S$; the molecular weight is 445.55; the structural formula is shown below:



Glipizide is a whitish, odorless powder with a melting point of 201-207°C (dec.) and a pKa of 5.9. It is insoluble in water and alcohols, but soluble in 0.1 *N* NaOH; it is freely soluble in dimethylformamide. GLUCOTROL tablets for oral use are available in 5 and 10 mg strengths.

CLINICAL PHARMACOLOGY

Mechanism of Action: The primary mode of action of GLUCOTROL in experimental animals appears to be the stimulation of insulin secretion from the beta cells of pancreatic islet tissue and is thus dependent on functioning beta cells in the pancreatic islets. In humans GLUCOTROL appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which GLUCOTROL lowers blood glucose during long-term administration has not been clearly established. In man, stimulation of insulin secretion by GLUCOTROL in response to a meal is undoubtedly of major importance. Fasting insulin levels are not elevated even on long-term GLUCOTROL administration, but the postprandial insulin response continues to be enhanced after at least 6 months of treatment. The insulinotropic response to a meal occurs within 30 minutes after an oral dose of GLUCOTROL in diabetic patients, but elevated insulin levels do not persist beyond the time of the meal challenge. Extrapancreatic effects may play a part in the mechanism of action of oral sulfonylurea hypoglycemic drugs.

Blood sugar control persists in some patients for up to 24 hours after a single dose of GLUCOTROL, even though plasma levels have declined to a small fraction of peak levels by that time (see Pharmacokinetics below).

Some patients fail to respond initially, or gradually lose their responsiveness to sulfonylurea drugs, including GLUCOTROL. Alternatively, GLUCOTROL may be effective in some patients who have not responded or have ceased to respond to other sulfonylureas.

Other Effects: It has been shown that GLUCOTROL therapy was effective in controlling blood sugar without deleterious changes in the plasma lipoprotein profiles of patients treated for NIDDM.

In a placebo-controlled, crossover study in normal volunteers, GLUCOTROL had no antidiuretic activity, and, in fact, led to a slight increase in free water clearance.

Pharmacokinetics: Gastrointestinal absorption of GLUCOTROL in man is uniform, rapid, and essentially complete. Peak plasma concentrations occur 1-3 hours after a single oral dose. The half-life of elimination ranges from 2-4 hours in normal subjects, whether given intravenously or orally. The metabolic and excretory patterns are similar with the two routes of administration, indicating that first-pass metabolism is not significant. GLUCOTROL does not accumulate in plasma on repeated oral administration. Total absorption and disposition of an oral dose was unaffected by food in normal volunteers, but absorption was delayed by about 40 minutes. Thus GLUCOTROL was more effective when administered about 30 minutes before, rather than with, a test meal in diabetic patients. Protein binding was studied in serum from volunteers who received either oral or intravenous GLUCOTROL and found to be 98-99% one hour after either route of administration. The apparent volume of distribution of GLUCOTROL after intravenous administration was 11 liters, indicative of localization within the extracellular fluid compartment. In mice no GLUCOTROL or metabolites were detectable autoradiographically in the brain or spinal cord of males or females, nor in the fetuses of pregnant females. In another study, however, very small amounts of radioactivity were detected in the fetuses of rats given labelled drug.

The metabolism of GLUCOTROL is extensive and occurs mainly in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Less than 10% unchanged GLUCOTROL is found in the urine.

INDICATIONS AND USAGE

GLUCOTROL is indicated as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with non-insulin-dependent diabetes mellitus (NIDDM; type II), formerly known as maturity-onset diabetes, after an adequate trial of dietary therapy has proved unsatisfactory.

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

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

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

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

CONTRAINDICATIONS

GLUCOTROL 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 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

General

Renal and Hepatic Disease: The metabolism and excretion of GLUCOTROL may be slowed in patients with impaired renal and/or hepatic function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted.

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 GLUCOTROL and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of Control of Blood Glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue GLUCOTROL and administer insulin.

The effectiveness of any oral hypoglycemic drug, including GLUCOTROL, 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.

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 and of alternative modes of therapy. They should also be informed about 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. When such drugs are administered to a patient receiving GLUCOTROL, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving GLUCOTROL, the patient should be observed closely for loss of control. *In vitro* binding studies with human serum proteins 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 the clinical situation and in the use of GLUCOTROL with these drugs.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility: A twenty month study in rats and an eighteen 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 (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. If GLUCOTROL is used during pregnancy, it should be discontinued at least one month before the expected delivery date.

Nursing Mothers: Although it is not known whether GLUCOTROL is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If the drug is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

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

ADVERSE REACTIONS

In U.S. and foreign 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 are the most common reactions. Gastrointestinal complaints were reported with the following approximate incidence: nausea and diarrhea, one in seventy; constipation and gastralgia, one in one hundred. 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 seventy 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 reactions have been reported with sulfonylureas. In the mouse, GLUCOTROL pretreatment did not cause an accumulation of acetaldehyde after ethanol administration. Clinical experience to date has shown that GLUCOTROL has an extremely low incidence of disulfiram-like alcohol reactions.

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

Laboratory Tests: The pattern of laboratory test abnormalities observed with GLUCOTROL was similar to that for other sulfonylureas. Occasional mild to moderate elevations of SGOT, LDH, alkaline phosphatase, BUN and creatinine were noted. One case of jaundice was reported. The relationship of these abnormalities to GLUCOTROL is uncertain, and they have rarely been associated with clinical symptoms.

OVERDOSAGE

There is no well documented experience with GLUCOTROL overdosage. The acute oral toxicity was extremely low in all species tested (LD_{50} greater than 4 g/kg).

Overdosage of sulfonylureas including GLUCOTROL can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. 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 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, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of an adequate blood-glucose-lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels may also be of value in monitoring the patient's response to therapy.

Short-term administration of GLUCOTROL may be sufficient during periods of transient loss of control in patients usually controlled well on diet.

In general, GLUCOTROL 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, given before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg.

Titration: 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. If response to a single dose is not satisfactory, dividing that dose may prove effective. The maximum recommended once daily dose is 15 mg. Doses above 15 mg should ordinarily be divided and given before meals of adequate caloric content. 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. Total daily doses above 30 mg have been safely given on a b.i.d. basis to long-term patients.

In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions (see PRECAUTIONS section).

Patients Receiving Insulin: As with other sulfonylurea-class hypoglycemics, many stable non-insulin-dependent diabetic patients receiving insulin may be safely placed on GLUCOTROL. When transferring patients from insulin to GLUCOTROL, the following general guidelines should be considered:

For patients whose daily insulin requirement is 20 units or less, insulin may be discontinued and GLUCOTROL therapy may begin at usual dosages. Several days should elapse between GLUCOTROL (glipizide) titration steps.

For patients whose daily insulin requirement is greater than 20 units, the insulin dose should be reduced by 50% and GLUCOTROL therapy may begin at usual dosages. Subsequent reductions in insulin dosage should depend on individual patient response. Several days should elapse between GLUCOTROL titration steps.

During the insulin withdrawal period, the patient should test urine samples for sugar and ketone bodies at least three times daily. Patients should be instructed to contact the prescriber immediately if these tests are abnormal. In some cases, especially when patient has been receiving greater than 40 units of insulin daily, it may be advisable to consider hospitalization during the transition period.

Patients Receiving Other Oral Hypoglycemic Agents: As with other sulfonylurea-class hypoglycemics, no transition period is necessary when transferring patients to GLUCOTROL. Patients should be observed carefully (1-2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (e.g., chlorpropamide) to GLUCOTROL due to potential overlapping of drug effect.

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.

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

CAUTION: Federal law prohibits dispensing without prescription.

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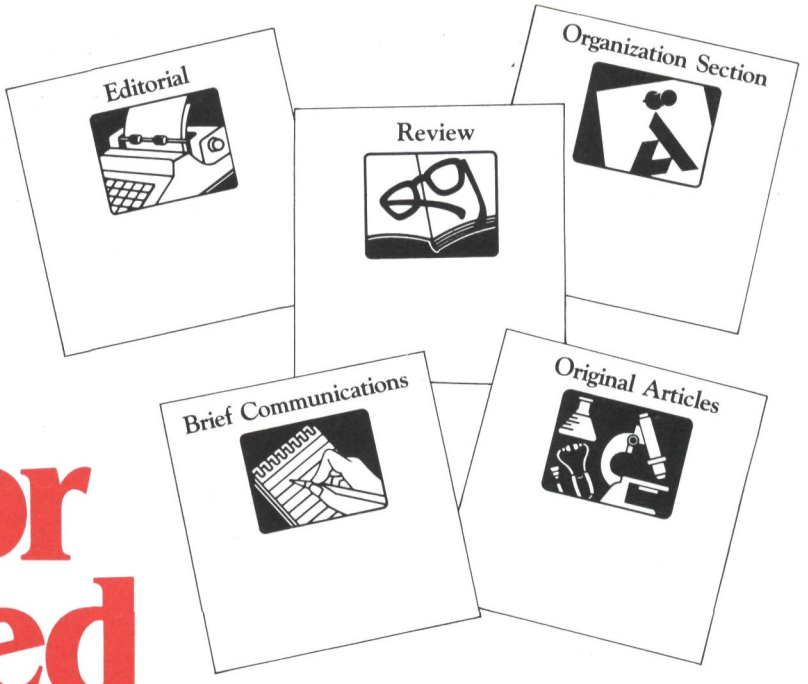

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