JULY 1984 VOLUME 33 NUMBER 7

diabetes

A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION®

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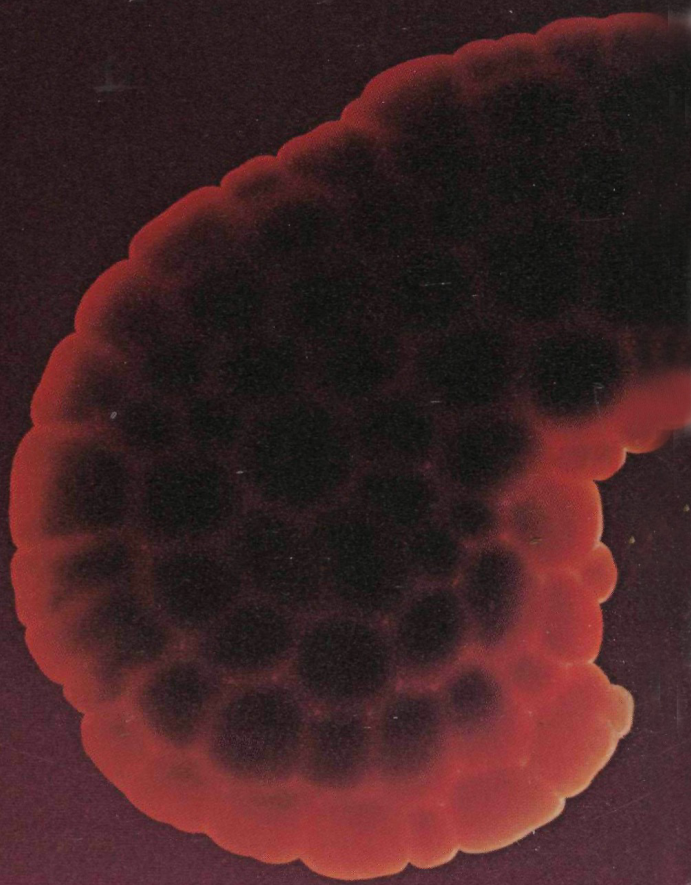
ISSN 0012-1797

Tolinase® Tablets and diet help put the
(tolazamide)

In most type II diabetic patients, insulin levels may be normal or even elevated, but glucose metabolism is less than normal. Tolinase Tablets pharmacologically influence the way the body metabolizes glucose.



The insulin paradox

The coexistence of normal or elevated insulin levels and elevated glucose levels is a common paradox in patients with type II (non-insulin-dependent) diabetes. This condition suggests a lack of tissue sensitivity to endogenous insulin–a phenomenon many investigators today refer to as cellular insulin resistance.

The failure of normal or above-normal amounts of endogenous insulin to produce a normal response in terms of glucose metabolism is believed to result most often from one or more underlying factors, such as beta-cell defects (inadequate or delayed initial response), defects at the cellular receptor and/or postreceptor level, or hepatic defects.

Initial therapy: A rational approach

Since insulin insufficiency is probably not the basic problem in type II diabetes, diet and exercise are considered the cornerstones of therapy because they help correct the cause of the underutilization of insulin (eg, receptor defect) and may help lower blood glucose. If diet and regular exercise fail to control glucose levels adequately, **Tolinase** Tablets are an appropriate addition to the regimen.

How Tolinase Tablets influence glucose metabolism

The primary mode of action of **Tolinase** Tablets is to lower serum glucose in responsive patients by stimulating the release of additional insulin **(1)**. As therapy continues, it is believed that **Tolinase** promotes peripheral glucose metabolism by helping to correct defects at the cellular receptor **(2)** and postreceptor **(3)** level. In this environment, tissue sensitivity and responsiveness to insulin increase, glucose levels decrease, and insulin levels frequently return toward normal.

Once-a-day dosage with Tolinase Tablets

has been shown to be just as effective as a divided dose in the treatment of non-insulin-dependent diabetes.

As with all sulfonylureas, hypoglycemia may occur. No sulfonylurea should be given to patients with serious kidney, liver, or endocrine disease. **Tolinase** is not indicated in patients with a history of repeated ketoacidosis or coma.

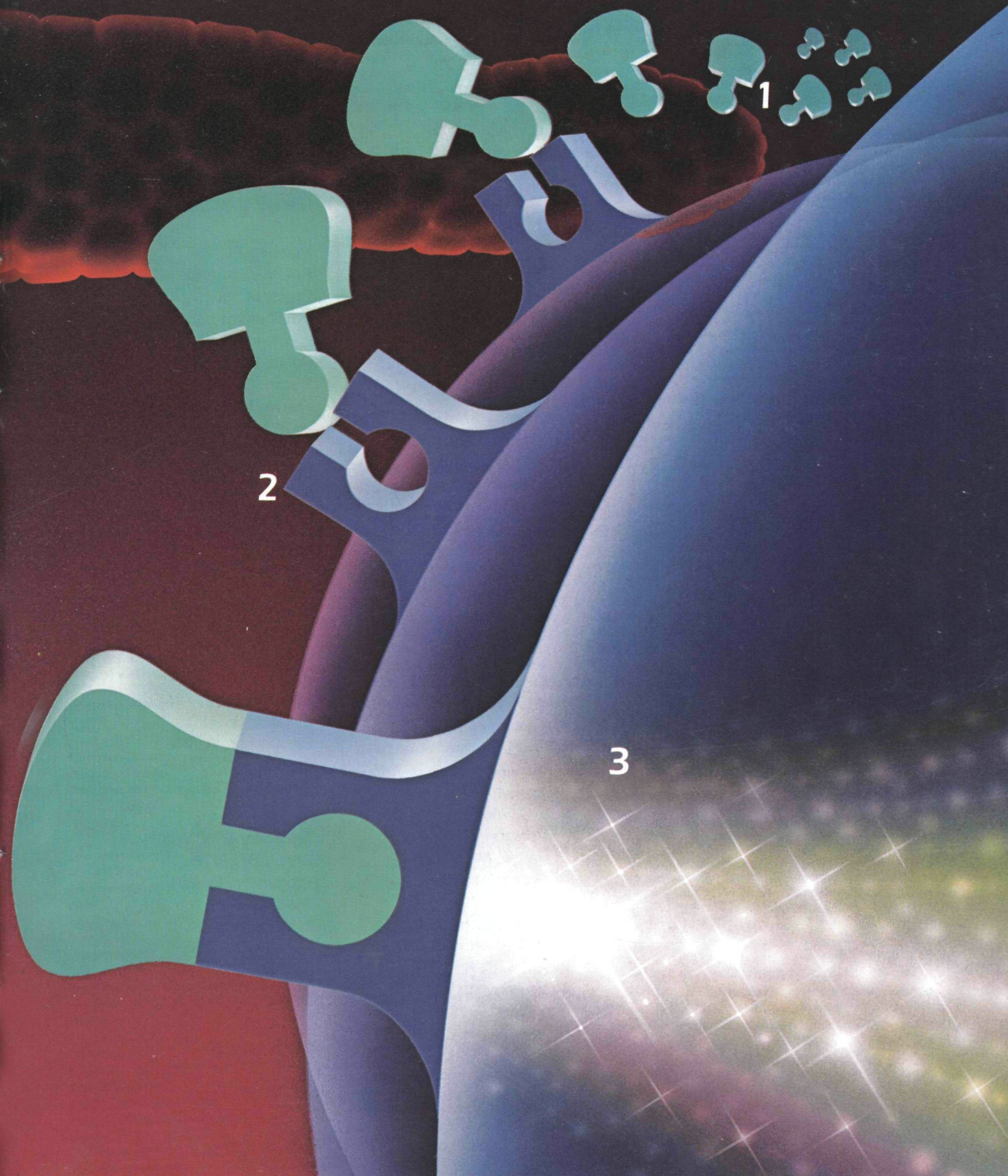
Tolinase® 100, 250 & 500 mg tablets
(tolazamide)

Once a day

For a brief summary of prescribing information, please turn the page.

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001

patient's own insulin back to work.



JULY AUTHOR INDEX

(Volume 33, Number 7)

diabetes

A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION®

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Manuscripts should be typewritten, with double spacing, and submitted in triplicate together with three copies of figures and photomicrographs. Manuscripts prepared in accord with the requirements specified in the document, "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," Annals of Internal Medicine 1982; 96:766–71, will be considered for publication.

References should be presented in the style of the following examples and numbered in order of appearance in the text: For Periodicals—Banting, F. G., and Best, C. H.: The internal secretion of the pancreas. J. Lab. Clin. Med. 1922; 7:251–66. For Books—Allen, Frederick M.: *Studies Concerning* Glycosuria and Diabetes. Cambridge, Harvard University Press, 1913:461.

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Galley proofs are sent to the principal author with a price list and order blank for reprints.

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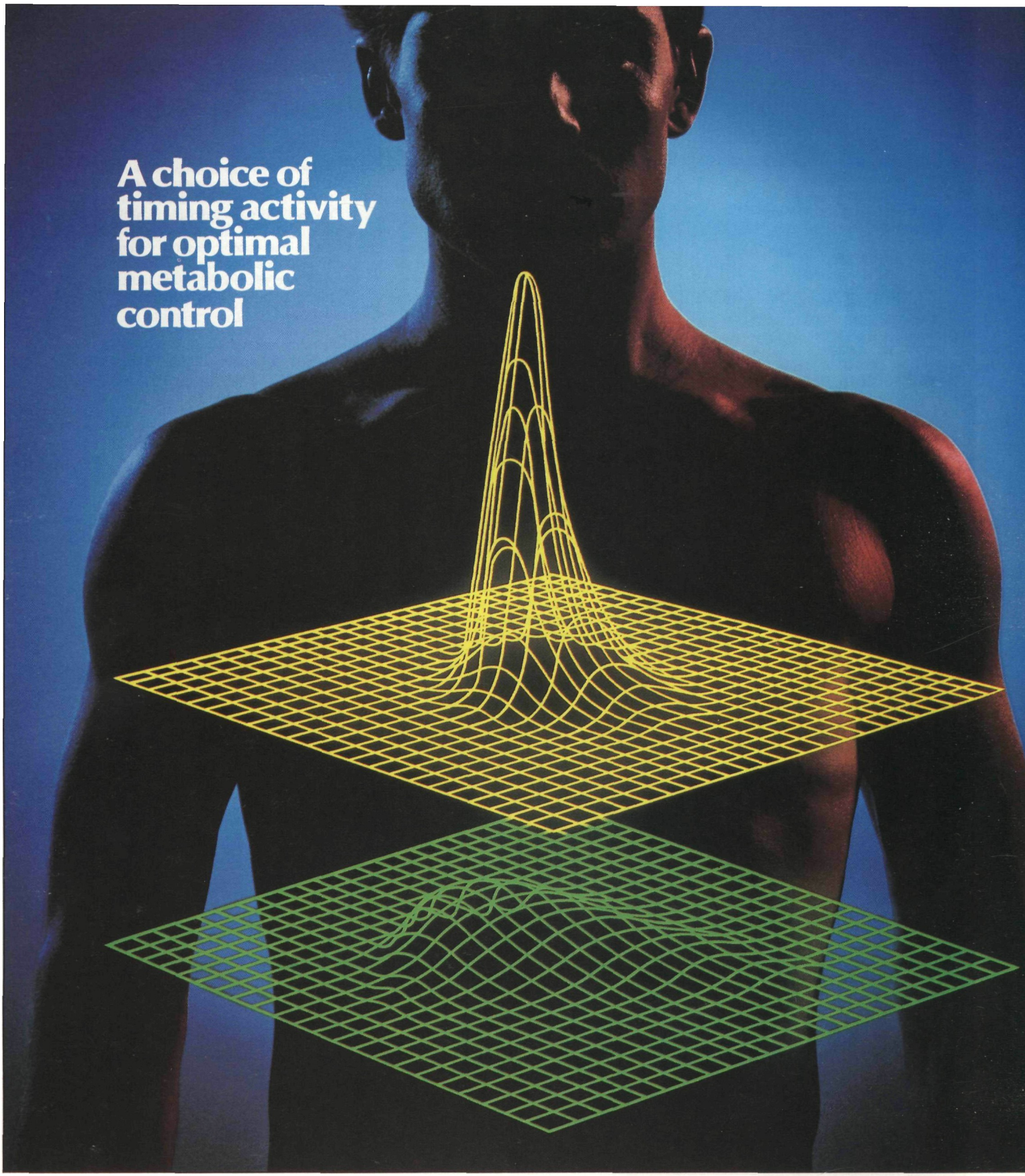
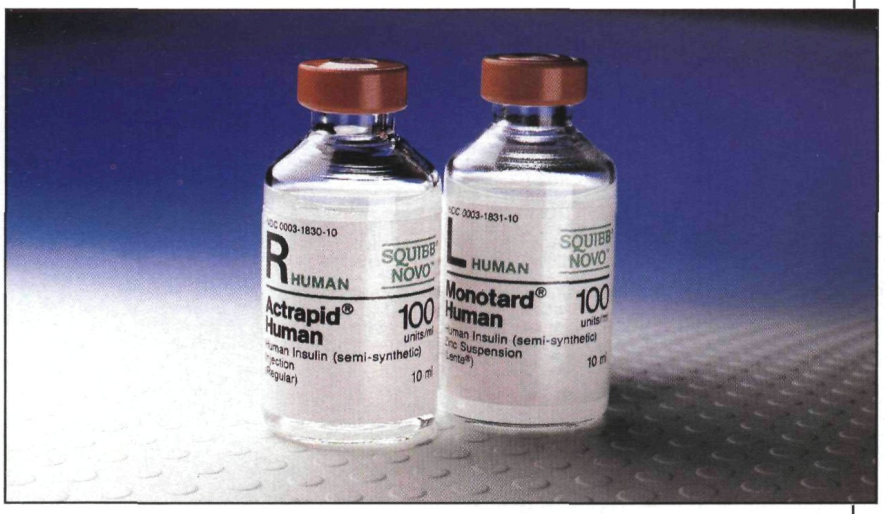


SQUIBB®
NOVO™

Human insulins with a documented **pharmacokinetic** profile

Squibb-Novo Human Insulins are comparable to purified porcine insulin in potency, onset and duration of effect. As demonstrated in clinical trials, both insulins produced a similar effect on blood glucose levels and resulted in similar insulin, C-peptide and intermediary metabolite concentrations.[1]



ACTRAPID® HUMAN 100 units/ml Human Insulin (semi-synthetic) Injection (Regular)

MONOTARD® HUMAN 100 units/ml Human Insulin (semi-synthetic) Zinc Suspension (Lente®)

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Human insulins with demonstrated **clinical** safety and efficacy

Extensive clinical studies worldwide have shown that ACTRAPID® Human and MONOTARD® Human provide effective metabolic control.

And both human insulins have demonstrated clinical safety, as documented in the studies carried out to date.[2]

Human insulins with a distinct **immunologic** profile

In a study of 102 newly diagnosed insulin-dependent diabetic patients, both ACTRAPID® Human and MONOTARD® Human induced a lower anti-insulin immune response than purified porcine insulins.[3]

Human insulins for all insulin-dependent patients

References:

1. Owens DR, Jones MK, Hayes TM, et al: Human insulin: study of safety and efficacy in man. *Br Med J* 282:1264–1266, 1981.

2. Data on file, Squibb-Novo, Inc., Princeton, N.J.

3. Schernthaner G, Borkenstein M, Fink M, et al: Immunogenicity of human insulin (Novo) or pork monocomponent insulin in HLA-DR-typed insulin-dependent diabetic individuals. *Diabetes Care* 6(Suppl 1):43–48, 1983.

See adjacent page for brief summary.

SQUIBB®-NOVO™ HUMAN INSULINS

Actrapid® Human 100 units/ml
Human Insulin (semi-synthetic)
Injection (Regular)

Monotard® Human 100 units/ml
Human Insulin (semi-synthetic)
Zinc Suspension (Lente®)

BRIEF SUMMARY OF INFORMATION FOR THE PATIENT

A naturally occurring enzyme is used in a process which converts pork pancreas insulin into SQUIBB-NOVO Human Insulin. By this enzymatic transpeptidation process the amino acid *alanine is replaced by the amino acid threonine thus forming the human insulin molecule.*

This human insulin (semi-synthetic) has undergone unique purification processes and is characterized by being structurally identical to the insulin produced by the human pancreas.

WARNING

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN PURITY, STRENGTH, BRAND (MANUFACTURER), TYPE (REGULAR, NPH, LENTE, ETC.) AND/OR SPECIES (ANIMAL OR HUMAN) MAY RESULT IN THE NEED FOR A CHANGE IN DOSAGE. THUS WHEN YOU CHANGE TO ACTRAPID® HUMAN OR MONOTARD® HUMAN INSULIN, A CHANGE IN DOSAGE MAY BE REQUIRED. IF AN ADJUSTMENT IS NEEDED IT WILL BECOME APPARENT EITHER WITHIN THE FIRST FEW DAYS OR OVER A PERIOD OF SEVERAL WEEKS.

TYPES OF INSULIN:

Actrapid® Human (Human Insulin (semi-synthetic) Injection) (Regular) has a short duration of activity. It is a clear, colorless solution. Its effect is rapid and it has a relatively short duration of activity (approximately 6 to 8 hours).

Monotard® Human (Human Insulin (semi-synthetic) Zinc Suspension) (Lente®) has an intermediate duration of activity. It is a cloudy suspension of crystalline and amorphous insulin particles (the cloudy material). Its effect starts more slowly and its duration of activity is longer (approximately 22 hours). The insulin substance (the cloudy material) settles at the bottom of the vial. Gently agitate so that the contents *are uniformly mixed before filling the syringe (see further instructions in the full* patient insert provided with the product).

Note: Preparations of insulin suspensions which are injected slowly may clog the tip of the needle, resulting in an inability to complete the injection. Because "syringe plugging" does not occur when the drug is injected more rapidly, the dose should be injected over 2–4 seconds.

All SQUIBB-NOVO human insulins are made in one strength, U-100. This means *that each milliliter (ml) contains 100 units of insulin. You should always use a syringe* which is marked for use with U-100 insulin.

STORAGE: Insulin should be stored in a cold place (between 36°F and 46°F) (2°C and 8°C) preferably in a refrigerator. **Do not let it freeze.** Keep the insulin vial in its carton so that it will stay clean and protected from light. Insulin which is in everyday use should be kept in the coolest practical place if storage in a refrigerator is impractical.

Never use insulin after the expiration date which is printed on the label.

Never use a vial of **Actrapid® Human** if it becomes viscous or has become other than water-clear and colorless.

Never use a vial of **Monotard® Human** if the precipitate (the white deposit in the bottom of the vial) has become lumped or granular in appearance or has formed a deposit of solid particles on the wall of the vial. Also this insulin should not be used if it remains clear after the vial has been gently agitated.

Once the rubber has been punctured a vial should be used for no more than a few weeks.

ADDITIONAL WARNINGS

1. If your physician has recommended a mixture of two types of insulin:
   —do not change the order of mixing your physician has advised;
   —do not change the type of syringe recommended.

This is because insulin syringes may vary in the amount of space between the bottom *line and the needle ("dead space"). Dosage errors may result from failure to follow* this advice.

2. You should take care not to inject your insulin into a muscle or into a vein.

INSULIN REACTIONS: An insulin reaction (hypoglycemia) can occur if you take too much insulin, miss meals, take more exercise than usual, work too hard, become ill (especially with vomiting or fever) or if your body's need for insulin is decreased.

The first symptoms of an insulin reaction usually come on suddenly and may *include a cold sweat, rapid heart beat, nervousness or "shakiness." These symptoms* may progress leading to loss of consciousness. Progression of these symptoms may be prevented by immediately taking sugar or a sugar sweetened product. If an insulin reaction has led to loss of consciousness or you have experienced repeated reactions, you should contact your physician.

DIABETIC ACIDOSIS AND COMA: Diabetic acidosis may develop if you take less insulin than you need. The most common causes are acute illness or infection, *omission of insulin doses or the injection of a smaller insulin dose than that* prescribed by your physician. A developing diabetic acidosis will be revealed by urine tests which show large amounts of sugar and acetone. The symptoms of thirst, large urine volumes, loss of appetite and fatigue come on gradually, usually over a period of some hours or days. If you notice such symptoms, contact your physician immediately.

ADVERSE REACTIONS: In a few diabetics, the skin where insulin has been injected may become red, swollen, and itchy. This is called a "local reaction." It may occur if the injection is not properly made, if the skin is sensitive to the cleansing solution (this is less likely to happen if isopropyl alcohol, 91%, is used), or if the patient is allergic to insulin. If you have a local reaction, notify your physician.

Insulin allergy rarely occurs but when it does, it may cause a serious reaction including a general skin rash over the body, shortness of breath, fast pulse, sweating, and a drop in blood pressure. If any of these symptoms develop, you should be seen *immediately by a physician.*

IMPORTANT NOTES

1. Never change from one insulin preparation to another without instructions from your physician. A mistake in the type, strength or species of insulin preparation could result in serious effects.
2. If you experience an acute illness, especially with vomiting or fever, test your urine for sugar and acetone, noting the results. Contact your physician for advice on adjustment to your insulin dosage.

If you are in any doubt about your condition, consult your physician.

For information contact: SQUIBB-NOVO, Inc.

Manufactured in Denmark by NOVO INDUSTRI A/S, Bagsvaerd, Denmark

Distributed by E. R. SQUIBB & SONS, Inc.
Princeton, NJ 08540

Date of Issue: November 1982

SQUIBB® NOVO™ **Squibb-Novo, Inc.**
120 Alexander Street
Princeton, New Jersey 08540

BRIEF SUMMARY
DIABINESE®(chlorpropamide) Tablets

Contraindications: Diabinese is not indicated in patients *having juvenile or growth-onset diabetes mellitus, severe* or unstable "brittle" diabetes, and diabetes complicated by ketosis and acidosis, diabetic coma, major surgery, severe infection, or severe trauma.

Diabinese is contraindicated during pregnancy. Serious consideration should be given to the potential hazard of its use in women of childbearing age who may become pregnant.

Diabinese is contraindicated in patients with serious impairment of hepatic, renal, or thyroid function.

Precautions: Use chlorpropamide with caution with barbiturates, *in patients with Addison's disease or in those* ingesting: alcohol, antibacterial sulfonamides, thiazides, phenylbutazone, salicylates, probenecid, dicoumarol or MAO inhibitors. Adequate dietary intake should be assured in all patients using Diabinese.

Warnings: DIABINESE (CHLORPROPAMIDE) SHOULD NOT BE USED IN JUVENILE DIABETES OR IN DIABETES COMPLICATED BY ACIDOSIS, COMA, SEVERE INFECTION, MAJOR SURGICAL PROCEDURES, SEVERE TRAUMA, SEVERE DIARRHEA, NAUSEA AND VOMITING, ETC. HERE, INSULIN IS INDISPENSABLE. HYPOGLYCEMIA, IF IT OCCURS, MAY BE PROLONGED. (SEE ADVERSE REACTIONS.) IN INSTANCES OF CONCOMITANT USE WITH INSULIN, PATIENTS SHOULD BE CAREFULLY MONITORED.

Adverse Reactions: Usually dose-related and generally respond to reduction or withdrawal of therapy. Generally transient and not of a serious nature and include anorexia, *nausea, vomiting and gastrointestinal intolerance; weak*ness and paresthesias.

Certain untoward reactions associated with idiosyncrasy or hypersensitivity have occasionally occurred, including jaundice, skin eruptions rarely progressing to erythema multiforme and exfoliative dermatitis, and probably depression of formed elements of the blood. They occur characteristically during the first six weeks of therapy. With a few exceptions, these manifestations have been mild and readily reversible on the withdrawal of the drug.

The more severe manifestations may require other therapeutic measures, including corticosteroid therapy.

Diabinese should be discontinued promptly when the development of sensitivity is suspected.

Jaundice has been reported, and is usually promptly reversible on discontinuance of therapy. THE OCCURRENCE OF PROGRESSIVE ALKALINE PHOSPHATASE ELEVATION SHOULD SUGGEST THE POSSIBILITY OF INCIPIENT JAUNDICE AND CONSTITUTES AN INDICATION FOR WITHDRAWAL OF THE DRUG.

Leukopenia, thrombocytopenia and mild anemia, which occur occasionally, are generally benign and revert to normal, following cessation of the drug.

Cases of aplastic anemia and agranulocytosis, generally similar to blood dyscrasias associated with other sulfonylureas, have been reported.

BECAUSE OF THE PROLONGED HYPOGLYCEMIC ACTION OF DIABINESE, PATIENTS WHO BECOME HYPOGLYCEMIC DURING THERAPY WITH THIS DRUG *REQUIRE CLOSE SUPERVISION FOR A MINIMUM* PERIOD OF 3 TO 5 DAYS, during which time frequent feedings or glucose administration are essential. The anorectic patient or the profoundly hypoglycemic patient should be hospitalized.

Rare cases of phototoxic reactions have been reported.

Edema associated with hyponatremia has been infre*quently reported. It is usually readily reversible when* medication is discontinued.

Dosage: 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. The mild to moderately severe, middle-aged, stable diabetic should be started on 250 mg daily. Because the geriatric diabetic patient appears to be more sensitive to the hypoglycemic effect of sulfonylurea drugs, older pa*tients should be started on smaller amounts of Diabinese,* in the range of 100 to 125 mg daily.

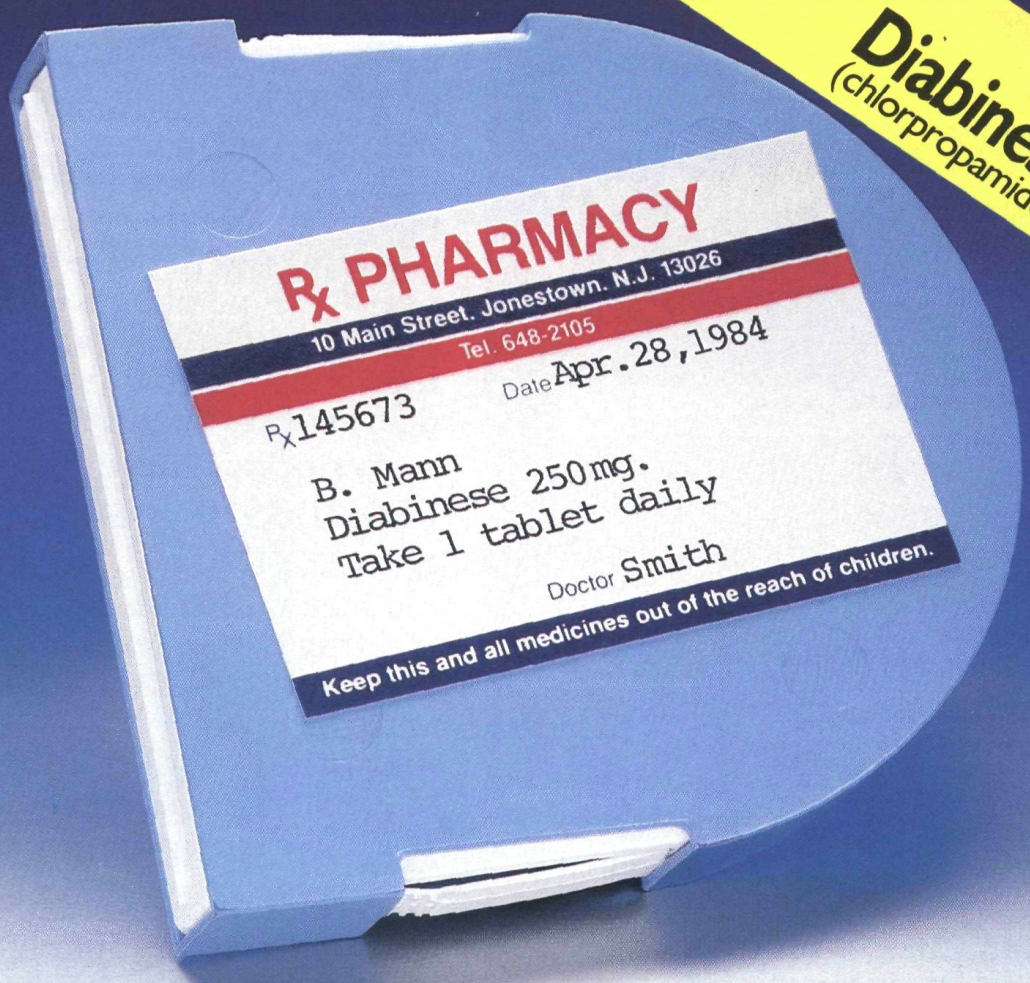
After five to seven days following initiation of therapy, dosage may be adjusted upward or downward in increments of 50 to 125 mg at intervals of three to five days.

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.

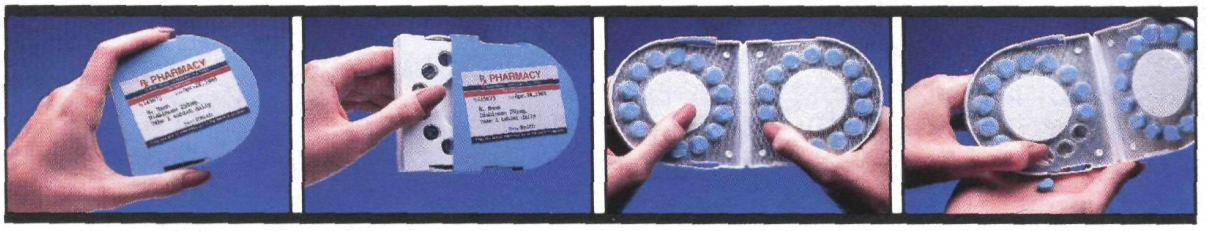
Supply: 100 mg and 250 mg, blue, 'D'-shaped, scored tablets.

More detailed professional information available on request.

Pfizer
LABORATORIES DIVISION
PFIZER INC.



The Case for Compliance



Introducing the Diabinese® (chlorpropamide) Tablets 250 mg D-Pak: a convenient new way for patients to remember and keep track of every once-a-day dose.

The Diabinese D-Pak (dispenser pack) contains a full 4-week supply of Diabinese 250-mg tablets in a lightweight, D-shaped, compact case. Inside, the distinctive blue, D-shaped tablets are arranged in easy-to-follow circles under clear day-of-the-week headings. So it is almost impossible to accidentally skip or repeat a dose. The Diabinese D-Pak is particularly beneficial to the newly diagnosed NIDDM patient who is a dietary failure, since compliance with a new therapeutic regimen can be a problem.

Next time you prescribe Diabinese 250 mg *q.d.* specify the

Diabinese® D-Pak
(chlorpropamide) Tablets 250 mg

Pfizer LABORATORIES DIVISION
PFIZER INC.

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

NEW WINNING PRICE!

Why not the best?

Accu-Chek™ bG

Blood Glucose Monitor

Needs no water—

Just wipe the test strip with a dry cotton ball 60 seconds after applying the drop of blood. Other strips require an inconvenient water wash.

A cinch to calibrate—

Insert the calibration film strip and an unused test strip and close the test strip door. That's it—the unit is calibrated and ready to use. No need to recalibrate until a new vial of strips is opened.

Simple to use—

Turn on the unit (no warm-up time). Put a drop of blood on the test strip, start the built-in timer, wipe the strip, insert it and read the blood glucose value in the window. Switch the unit off (if you forget, it turns off automatically after 3 minutes). That's all.

Accurate—

Digital readout gives an exact numerical value. Mini-computer and calibration for each vial of strips insures accuracy. Any malfunction or procedural error is reported on the digital readout.

Portable—

Battery operated, small and lightweight, needs no outside power supply, so it's easy to carry anywhere.

Affordable—

Accu-Chek bG is competitively priced, and purchase is covered by most third-party payment plans.

A winning combination with Chemstrip bG®

One strip...one system—

Best of all, the test strip used is Chemstrip bG. Now there is the option of visual or digital readings—or both. The unit can be used to check and improve the accuracy of visual readings, or for those who prefer or need a number. And the Accu-Chek bG meter will read the test strip accurately up to 7 days after the blood sample is taken, when used test strips are stored properly. Chemstrip bG and Accu-Chek bG...a winning combination for accuracy and flexibility to meet all needs.

Bio-Dynamics
A Boehringer Mannheim Division
9115 Hague Road, Indianapolis, IN 46250

mannheim boehringer

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

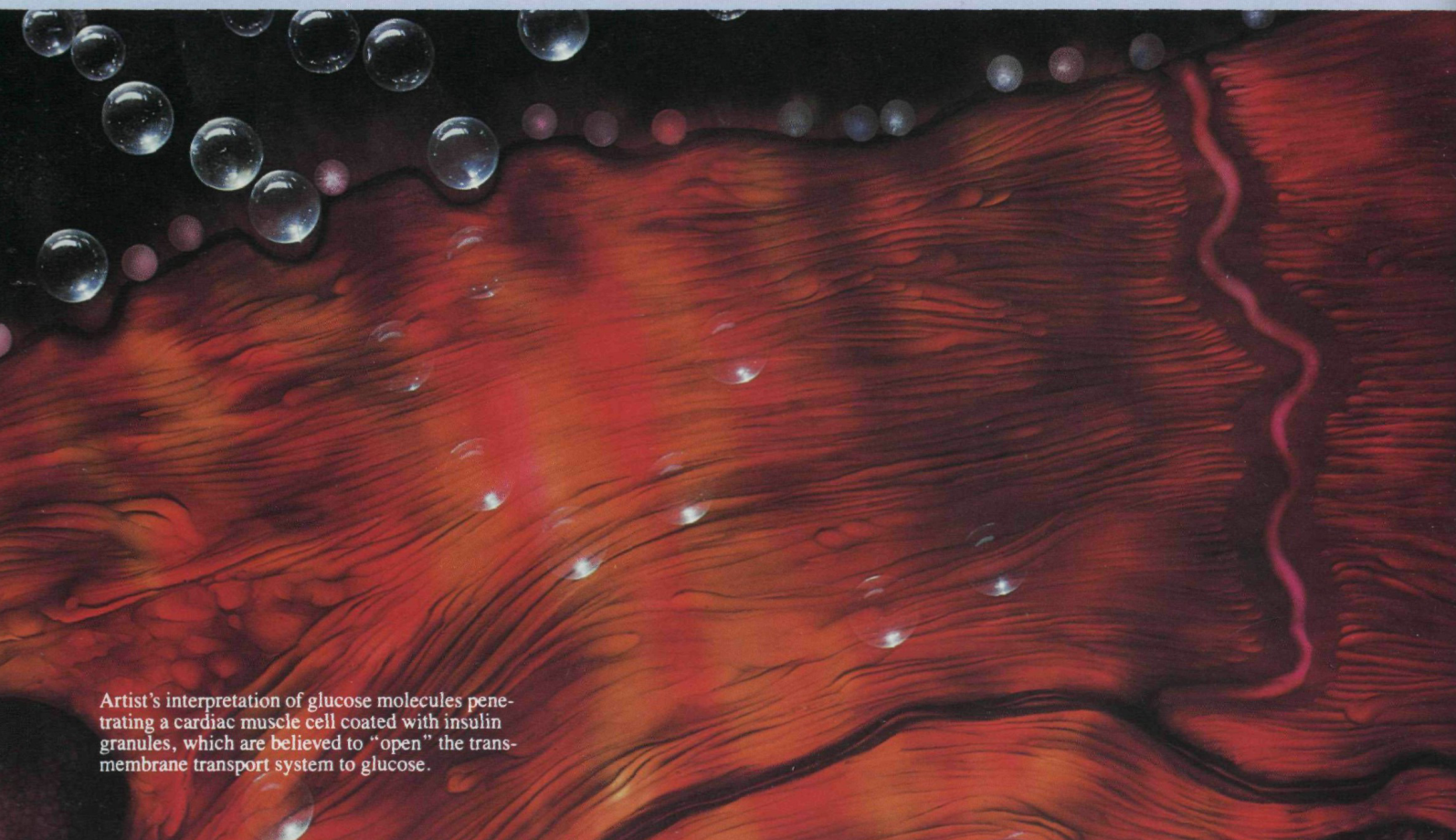
Inadequate secretion of insulin by pancreatic beta cells and impaired insulin action at target cells appear to be basic pathophysiologic abnormalities in NIDDM.[1-3] Although the mechanism of action is still under investigation, it appears that Glucotrol may exert its antidiabetic effect not only by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

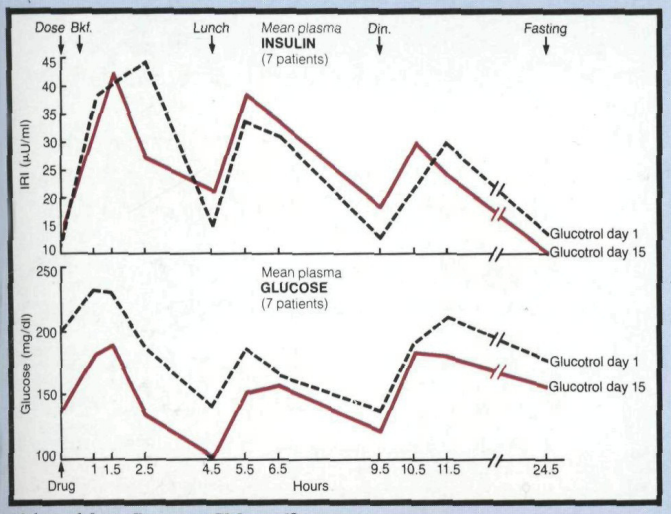


Artist's interpretation of glucose molecules penetrating a cardiac muscle cell coated with insulin granules, which are believed to "open" the transmembrane transport system to glucose.

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.

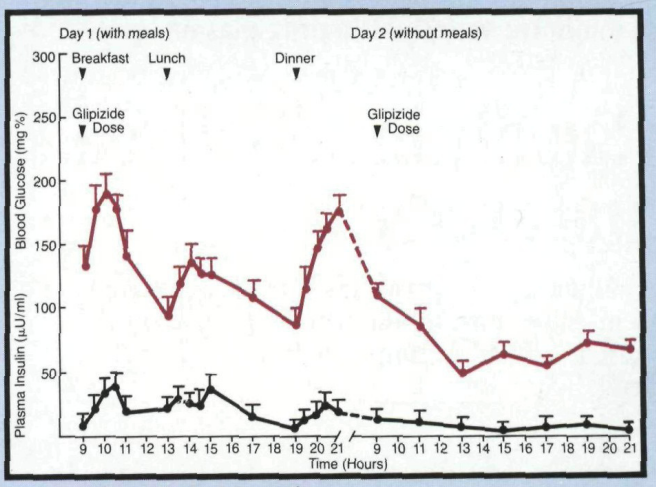


(Adapted from Peterson CM, et al[7])

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])

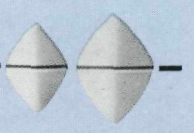
Mean values of blood glucose in mg/100 ml and I.R.I. in μU/ml plotted against time for six diabetics treated with a single morning dose of Glucotrol (glipizide), 5 to 10 mg, with standard diet on day one and no meals on day two. Even on day two, no hypoglycemic reactions were reported by any of these 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

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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.

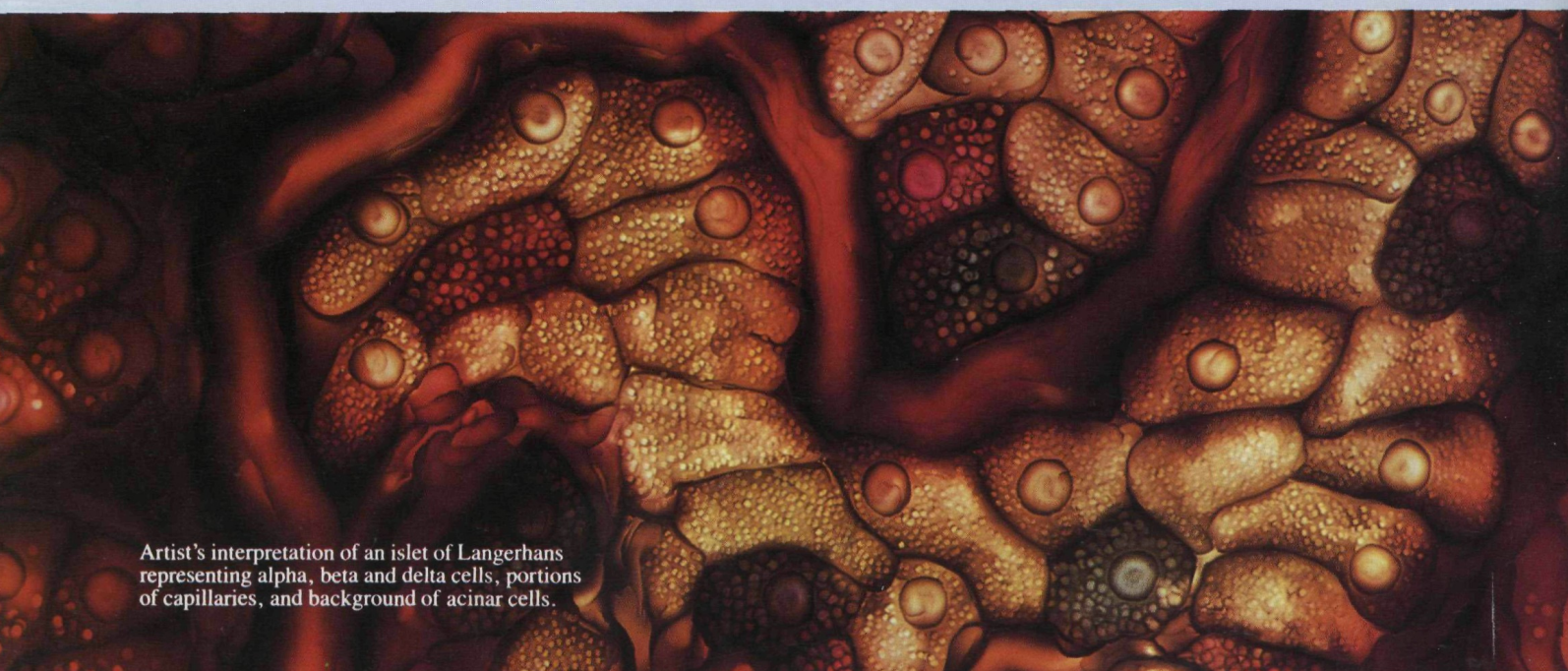
While controversy remains in the findings of UGDP, there have been reports of increased cardiovascular risk associated with oral hypoglycemic therapy.

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:

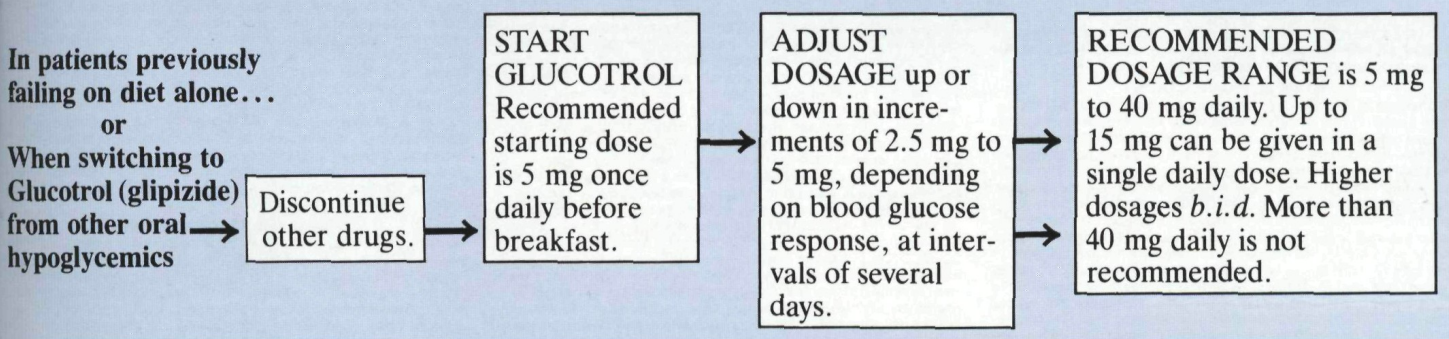
1. Reaven GM, Bernstein R, Davis B, et al: Nonketotic diabetes mellitus: Insulin deficiency or resistance? *Am J Med* 1976; 60:80-88. **2.** Defronzo R, Diebert D, Hendler R, et al: Direct evidence of insulin resistance in maturity-onset diabetes. *Diabetes* 1978; 27(Suppl 1): Abstract 4. **3.** Lohmann 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.

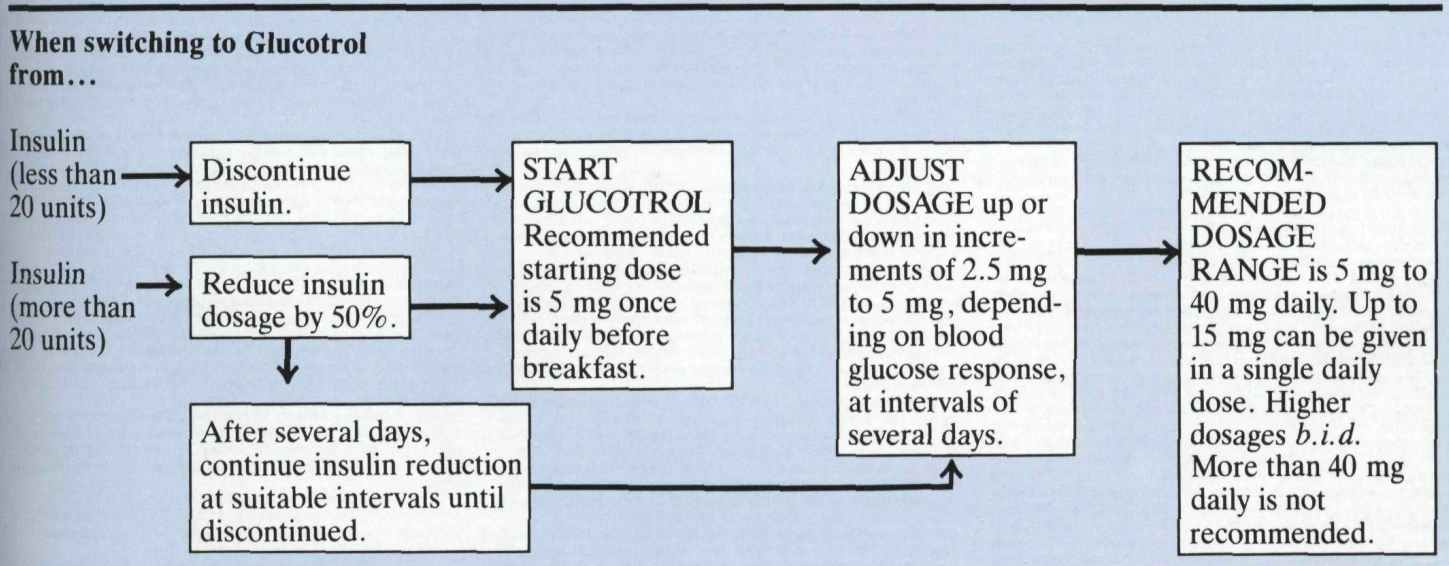


Artist's interpretation of an islet of Langerhans representing alpha, beta and delta cells, portions of capillaries, and background of acinar cells.

Convenient dosage regimen

Dosage Guide



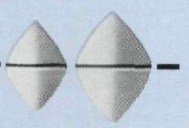


New

When diet alone fails in NIDDM

Glucotrol®

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



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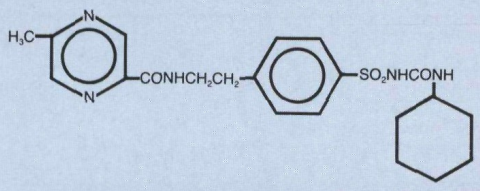
GLUCOTROL® (glipizide) TABLETS

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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- The Berson Memorial Lecture: Insulin - glucagon relationships in the defense against hypoglycemia by Roger H. Unger
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diabetes will tell you!

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Orinase helps restore blood sugar to more normal ranges with as little as 250 mg per day in some elderly diabetic patients.

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Orinase is not indicated in type I diabetes, unstable brittle diabetes, or in diabetes complicated by acidosis, ketosis, or coma. Severe hypoglycemia, though uncommon, may occur.

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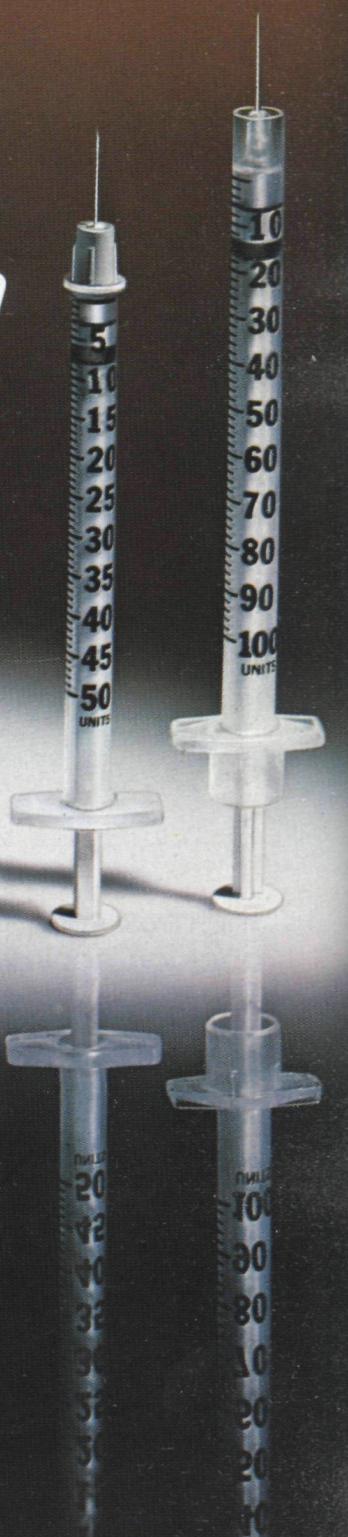
The Thinnest, Finest, Sharpest Needle For Unequalled Injection Comfort



The B-D MICRO-FINE III needle is a unique achievement in injection comfort—designed specifically to help assure increased compliance by your insulin-injecting patients.

Though the sharpness isn't visible to the naked eye, nationwide in-home use tests with hundreds of insulin users proved conclusively that patients could feel the remarkable comfort of the MICRO-FINE III needle.

Typical user comments: "It's like no injection at all"..."The needle just slips in"..."It's a much easier injection."

Finest Insulin Syringe Needle Ever Made

MICRO-FINE III is made with the highest quality surgical-grade stainless steel...then tempered and honed to incredible fineness and strength with a gracefully bevelled point. The result is the thinnest, finest, sharpest needle for *unequalled injection comfort.*

MICRO-BONDED® Lubrication For Extra Comfort

An exclusive B-D process keeps the lubrication on the needle after it has pierced the insulin vial stopper—and even during injection, to reduce needle drag for smoother, more effortless injections.

Only B-D Syringes Give Your Patients All Of These Special Advantages

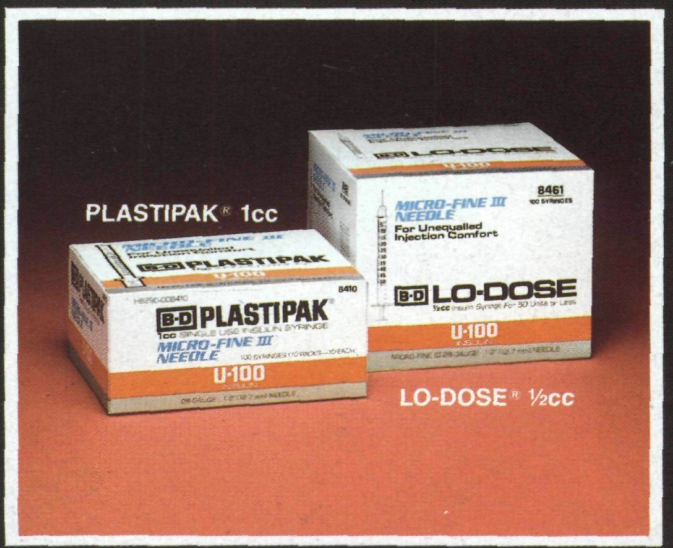
- *MICRO-FINE III Needle*...thinnest, finest, sharpest needle for unequalled injection comfort.
- *Larger, bolder scale numbers and markings*—so much easier to see, even with eyesight problems.
- *Single-scale markings for exact measurement*...following the recommendations of the American Diabetes Association.
- *THINLINE™ Plunger Tip* lines up precisely with the scale markings...makes it easier to fill syringe with the specific dose you prescribe.
- *No "dead space" in the needle hub or in the syringe.* That's how B-D makes mixing of insulins more precise—minimizes air bubbles, reduces insulin waste.

America's Most Preferred Insulin Syringe

B-D Insulin Syringes are recommended most by professionals, used most in hospitals, and overwhelmingly preferred by insulin users.

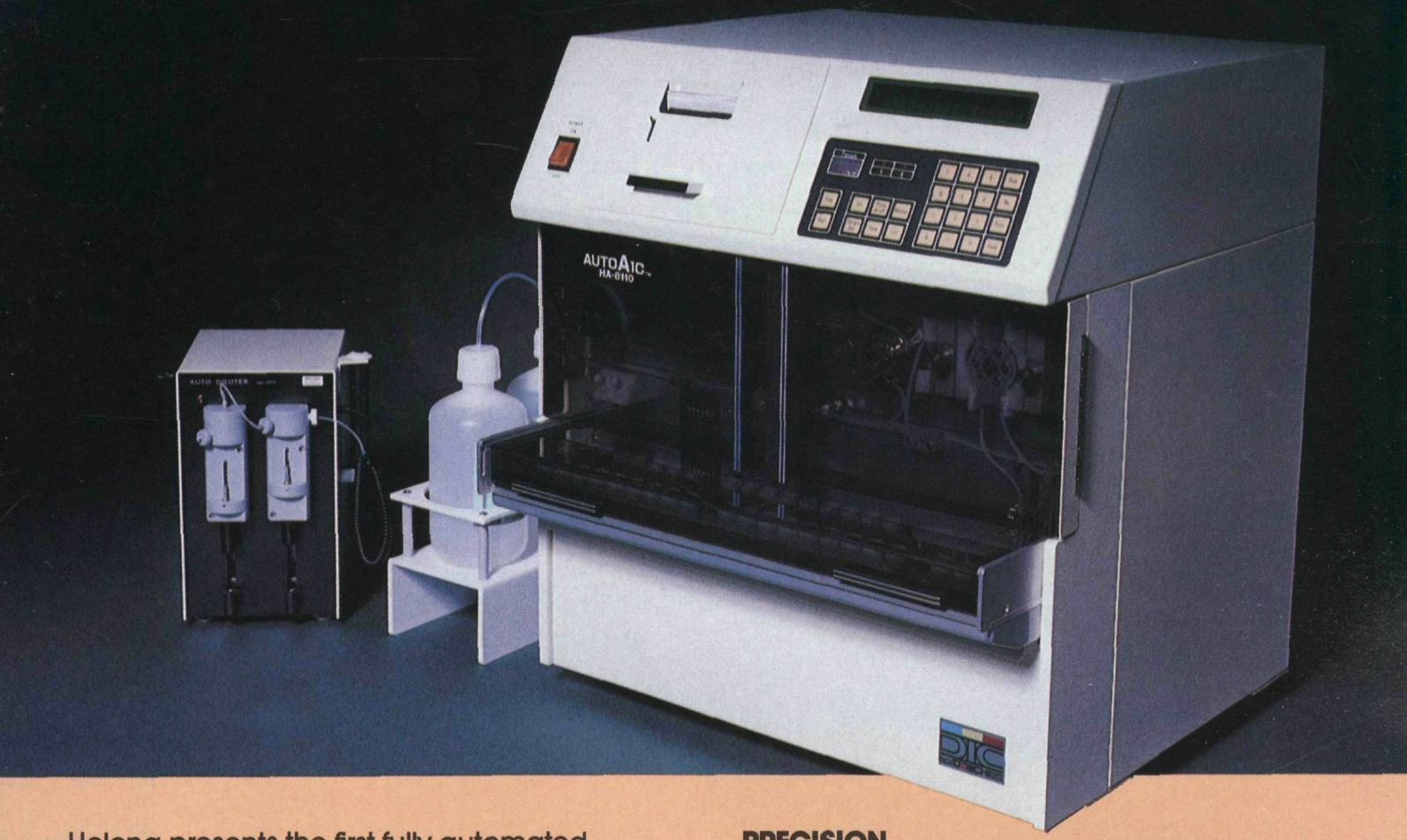
B-D Insulin Syringes with the MICRO-FINE III needle meet important syringe design specifications recommended by the American Diabetes Association to the United States Government.

The B-D MICRO-FINE III Needle—Unequalled Injection Comfort To Assure Greater Patient Compliance.

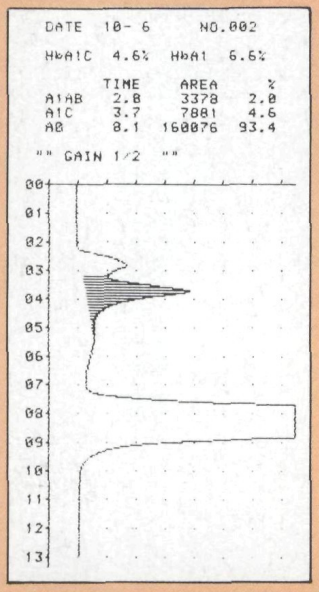


B-D Better Diabetes Care

NOW Precise Glycosylated Hemoglobin Measurement with Full Automation



Helena presents the first fully automated analyzer for glycosylated hemoglobin testing. Designed especially for the laboratory wanting consistently accurate answers and minimal labor costs. The HA-8110 utilizes state-of-the-art HPLC technology to give you



- **Precise Results**
- **Automatic Sampling, Injection and Detection**
- **Printed Report with Scan, Total A1, $A1_C$ Quantitation**
- **Savings in Time and Money**

Helena is the leading supplier of testing systems for glycosylated hemoglobins. Our full line includes the HPLC system, and kits for ion-exchange chromatography, affinity chromatography, and electrophoresis.

PRECISION

Based on studies of both normal and diabetic individuals, the HPLC method yields within-run and run-to-run C.V.'s of less than 4%. Precision, accuracy and reproducibility with this system are superior to any other method.

AUTOMATION

Automatically processes any batch size up to 50 samples —with no operator involvement after initial setup. Automatically prints out date, test number, HbA1c and total HbA1 results, and chromatographic pattern for each specimen.

EASE OF USE

Microcomputer technology and an easy to understand keyboard provide a system requiring minimal operator training. Monitors show operating system parameters at a glance. Built in memory stores up to 100 test results, retrievable at the touch of a button.

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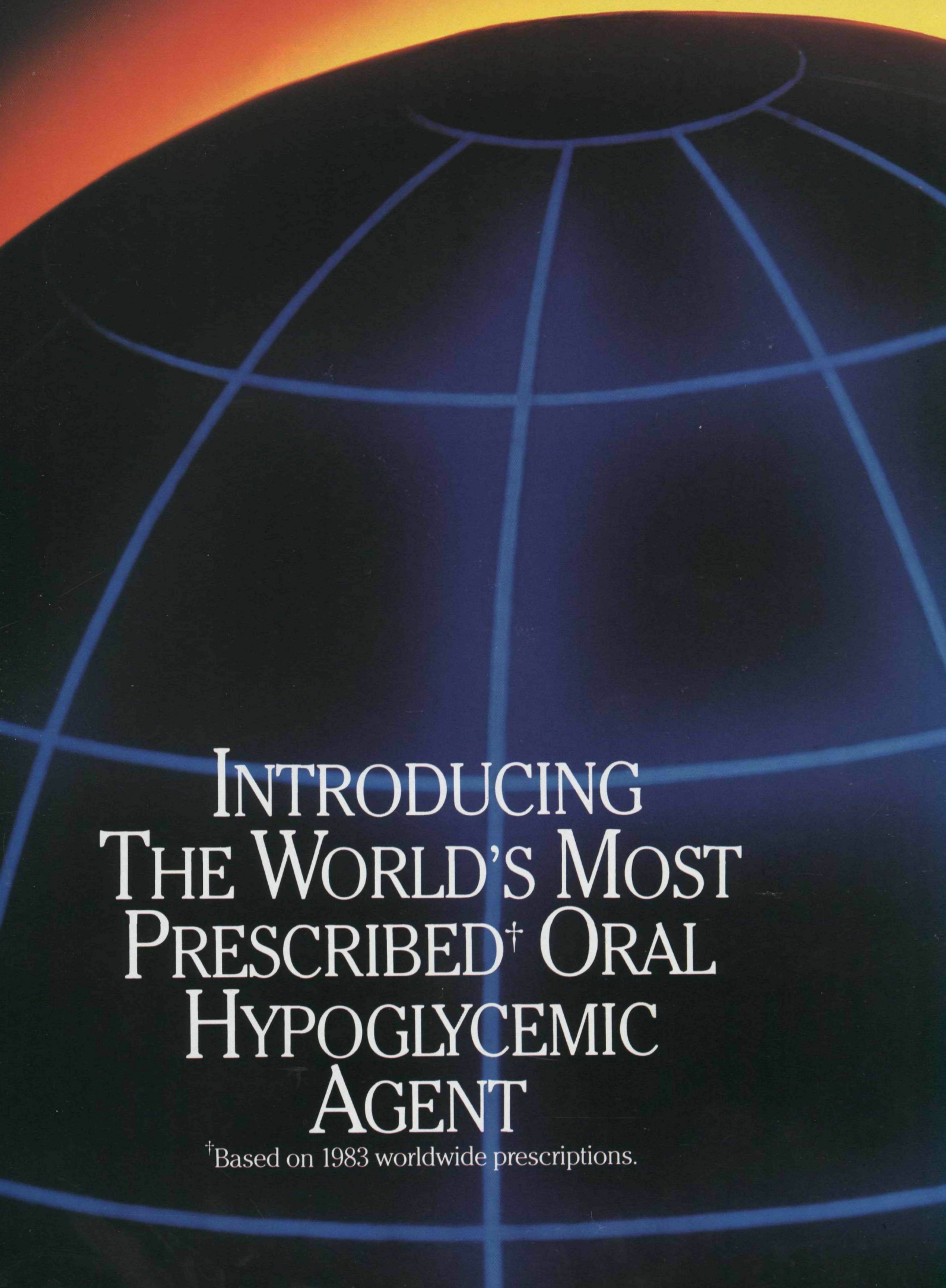
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THE WORLD'S MOST
PRESCRIBED† ORAL
HYPOGLYCEMIC
AGENT
†Based on 1983 worldwide prescriptions.

DIAβ
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TABLETS 1.25, 2.5 and 5 mg

As an adjunct to diet

WORLDWIDE LEADER† IN THE TREATMENT OF TYPE II** DIABETICS

†Based on 1983 worldwide prescriptions

**Non-Insulin-Dependent Diabetes Mellitus (NIDDM)

ETA®
RIDE*)

FOR GOOD REASONS

- ☐ Smooth control in most patients with a single daily dose.
- ☐ Low overall incidence of adverse reactions.
- ☐ No antidiuretic effects.
- ☐ Dual route of excretion.
- ☐ 14 years' worldwide experience in millions of patients.

In considering the use of DiaBeta,® consult the INDICATIONS AND USAGE, WARNINGS and PRECAUTIONS sections of the Prescribing Information, a brief summary of which appears on the last page of this advertisement. Dosage should be monitored in patients with hepatic or renal insufficiency to avoid hypoglycemia.

* Glyburide is the generic name for DiaBeta® in the U.S. and Canada. Glibenclamide is the generic name in other countries.

FROM THE ORIGINATORS OF TOLBUTAMIDE, HOECHST AG

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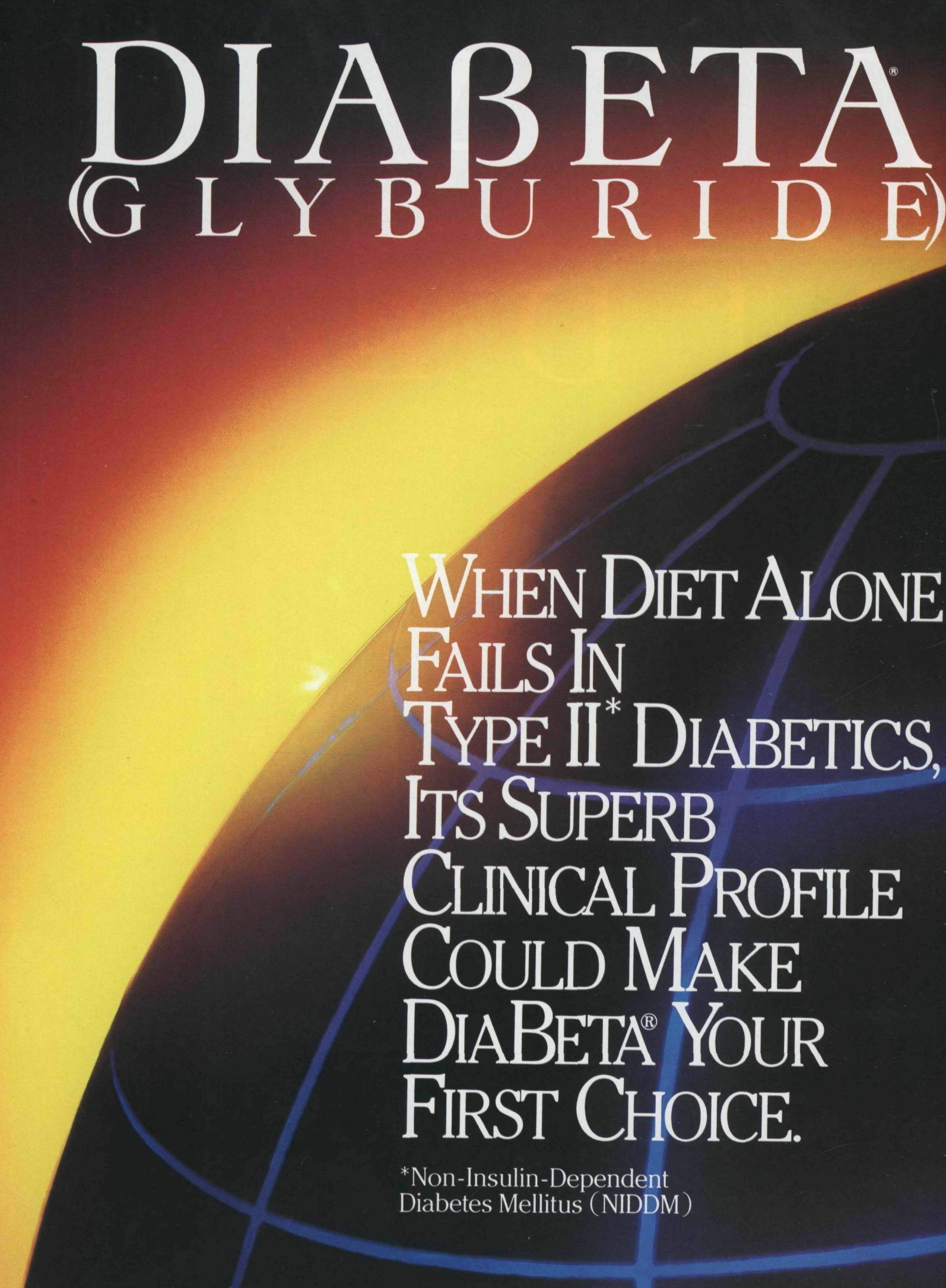
DIABETA®
(GLYBURIDE)



WHEN DIET ALONE FAILS IN TYPE II* DIABETICS, ITS SUPERB CLINICAL PROFILE COULD MAKE DIABETA® YOUR FIRST CHOICE.

*Non-Insulin-Dependent Diabetes Mellitus (NIDDM)

Convenient, Once-Daily Dosage Provides Smooth Control For Most Patients, Encourages Compliance.

The 10-hour half-life of DiaBeta® (glyburide) permits once-a-day dosage for most patients with normal meal patterns.

In one series of worldwide, multicenter clinical trials[1] among 3,952 patients, 3,144 could be maintained with 10 mg or less daily. Of these 3,144, 93.5% were maintained on just a single dose. Higher doses were usually divided to prevent hypoglycemic reactions.

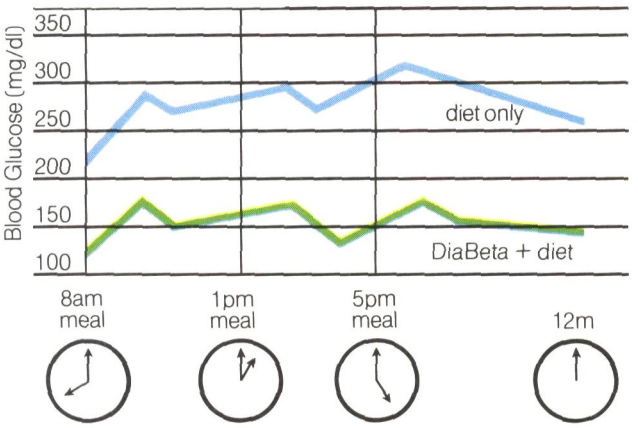
Insulin Levels Smoothly Parallel Blood Sugar Levels.

DiaBeta® (glyburide) stimulates prompt yet smooth insulin secretion in response to meals.[2]

The mechanism by which DiaBeta® (glyburide) lowers blood glucose during long-term administration has not been clearly established.

With chronic administration in Type II diabetic patients, the blood glucose lowering effect persists despite a gradual decline in the insulin secretory response to the drug. Extrapancreatic effects play a part in the mechanism of action.

Smooth Control



Adapted from O'Sullivan, D.J. and Cashman, W. F.: Blood glucose variations and clinical experience with glibenclamide in diabetes mellitus. BRIT. MED. J.2: 572-574(1970)

Mean blood glucose values for 25 patients (of 30) responding to a single dose of DiaBeta® given with breakfast.[3] Note comparability of glucose levels at midnight and early morning.

Of 30 patients, 14 were newly diagnosed; 14 were unsatisfactorily controlled with other oral hypoglycemic agents; two requested transfer from insulin. The five patients not responding to DiaBeta® (glyburide) had been treated previously with other oral hypoglycemic agents.

Worldwide Leader In The Treatment Of Type II Diabetics

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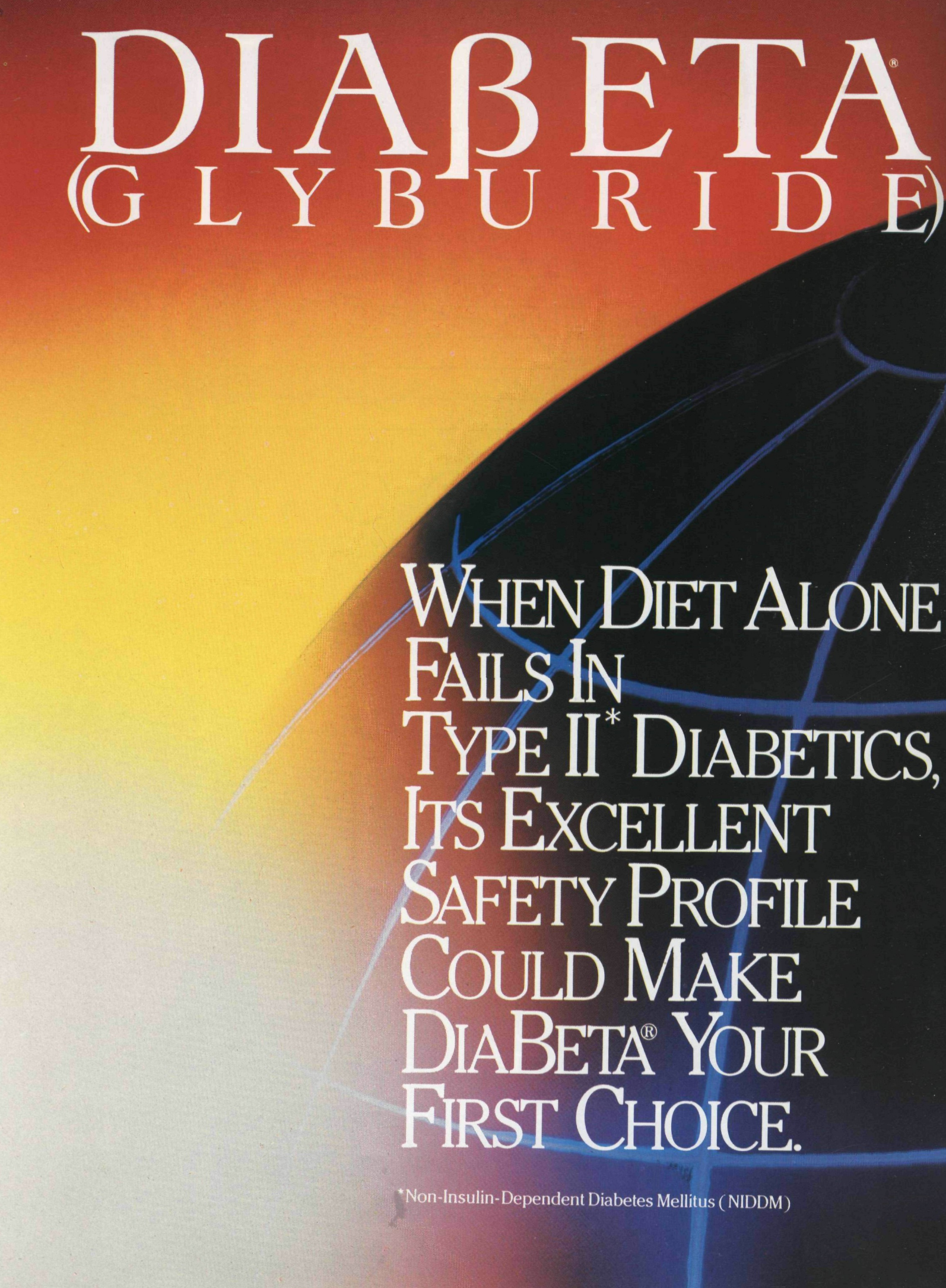
DIABETA®
(GLYBURIDE)



WHEN DIET ALONE FAILS IN TYPE II* DIABETICS, ITS EXCELLENT SAFETY PROFILE COULD MAKE DIABETA® YOUR FIRST CHOICE.

*Non-Insulin-Dependent Diabetes Mellitus (NIDDM)

Low Overall Incidence Of Adverse Reactions

The most common adverse reactions to DiaBeta® (glyburide) were gastrointestinal, occurring in 1.8% of patients in clinical trials. Most disappeared with dosage reduction. Dermatologic reactions occurred in 1.5% of patients, but were often transitory.[4]

All hypoglycemic agents, including insulin, are capable of producing severe hypoglycemia. DiaBeta® is a potent blood glucose lowering agent, effective at much lower doses than other sulfonylureas previously available. Proper patient selection, dosage and instructions are extremely important to avoid hypoglycemic episodes.

As with all sulfonylureas, other side effects, e.g., hematologic, may occur.

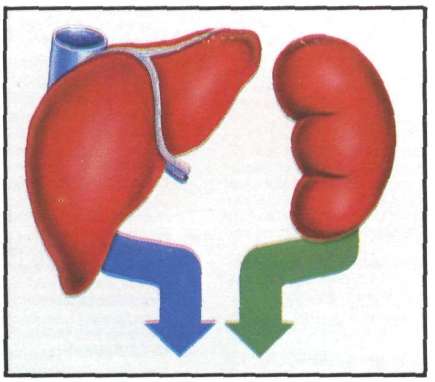
Please consult the SPECIAL WARNING on increased risk of cardiovascular mortality based on the UGDP study, and PRECAUTIONS and ADVERSE REACTIONS sections of Prescribing Information for details.

No antidiuretic effect.

DiaBeta® has been found to increase free water clearance in diabetics, resulting in slight diuresis. Chlorpropamide, by contrast, has been shown to increase water retention which may result in edema associated with hyponatremia.[5]

Dual Route Of Excretion May Afford Reduced Risk Of Accumulation

Most older sulfonylureas are excreted almost entirely via the urine.[6] However, only 50% of DiaBeta® (glyburide) is excreted via the urine; the other 50% is excreted via the bile.[7,8] Because elimination of the active drug and its metabolites is not solely dependent on renal function, the risk of accumulation and resulting hypoglycemia in patients with



nephropathy may be lessened. This is particularly important in view of the frequency of nephropathy in diabetic patients. Caution, of course, should be exercised in patients with renal or hepatic impairment. Hepatic insufficiency may diminish gluconeogenesis and also may cause elevated blood levels of DiaBeta,® both of which increase the risk of serious hypoglycemic reactions.

Worldwide Leader In The Treatment Of Type II Diabetics

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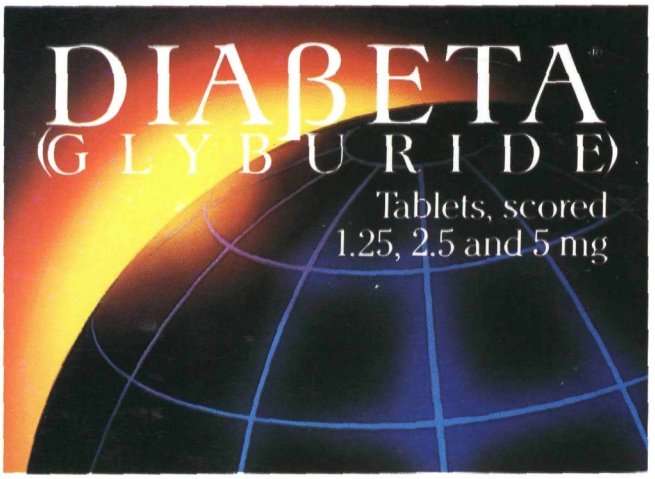
WORLDWIDE LEADER IN THE TREATMENT OF TYPE II DIABETICS



BRIEF SUMMARY

INDICATIONS AND USAGE

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

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

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

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

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

CONTRAINDICATIONS

DiaBeta® (glyburide) is contraindicated in patients with:

1. Known hypersensitivity to the drug.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

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

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

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

PRECAUTIONS:

General

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

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

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

Information for patients

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

DiaBeta® (glyburide) 5.0 mg tablet contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions in certain susceptible individuals.

Laboratory Tests

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

Drug Interactions

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

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

Pregnancy

Teratogenic Effects: Pregnancy Category B

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

Nonteratogenic Effects:

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

Nursing Mothers

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

PEDIATRIC USE

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

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

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

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

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

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

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

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

Of the thousands of papers published worldwide on glyburide, the following are referred to in this advertisement. Glyburide is the U.S. and Canadian generic name for glibenclamide.

1. Müller, R.: The clinical evaluation of an oral antidiabetic drug. AUSTR. N.Z. J. MED. 1 (Suppl. 2): 39-46 (1971).
2. Owens, D.R., Wragg, K.G., Shetty, K.T., Biggs, P.I., and Davies, C.D.: Glibenclamide, acute/long term response in M.O. diabetics. HORM. METAB. RES. 11, 411-412, 1979.
3. O'Sullivan, D.J. and Cashman, W.F.: Blood glucose variations and clinical experience with glibenclamide in diabetes mellitus. BRIT. MED. J. 2:572-574 (1970).
4. Data on file, Hoechst-Roussel Pharmaceuticals Inc.
5. Moses, A.M., Howanitz, J., and Miller, M.: Diuretic action of three sulfonylurea drugs. ANNALS INT. MED. 78, (4) 541-544, (1973).
6. Yetiv, J.Z., Bianchini, J.R. (Eds), Oral hypoglycemics. Recent advance in clinical therapeutics Vol. 1, Chap. 12. Academic Press, Continuing Medical Education Division, New York: 1981.
7. Rupp, W., Christ, O., and Fullberth, W.: Studies on the bioavailability of glibenclamide. ARZNEIM. FORSCH. 22: 471-473 (1972).
8. Christ, O., Heptner, W., and Rupp, W.: Investigations on absorption, excretion, and metabolism in man after administration of C-labeled HB 419. HORM. METAB. RES. 1 (Suppl.): 51-53 (1969).

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Introducing

the most up-to-date review of diabetes mellitus! It's **Diabetes Mellitus, Vol. V**, edited by Harold Rifkin, MD and Philip Raskin, MD. This comprehensive American Diabetes Association work contains articles by 67 top-flight diabetes experts in their specialty areas. Designed for endocrinologists, internists, family physicians or anyone involved in diabetes care, it's the most reliable review, giving you a full range of views and experiences to determine what's best for your patient.

This practical text explores the nature of diabetes, diagnosis and treatment and an evaluation of the impact of diabetes on the acutely ill and long-term patient.

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What's more, **Diabetes Mellitus, Vol. V** examines new topics and ideas not covered in previous volumes, such as somatostatin, neurogastrointestinal peptide hormones, insulin receptors and new concepts regarding the genetics of the disease. More than 50 illustrations, including tables, figures and photographs, visually enhance your understanding of the subject.

Complete review - stresses basic physiologic and biochemical mechanisms, provides a clearer understanding of the genetics of the disease and discusses existing and future therapeutic approaches.

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Referenced after each chapter for easy access to more in-depth information for further research.

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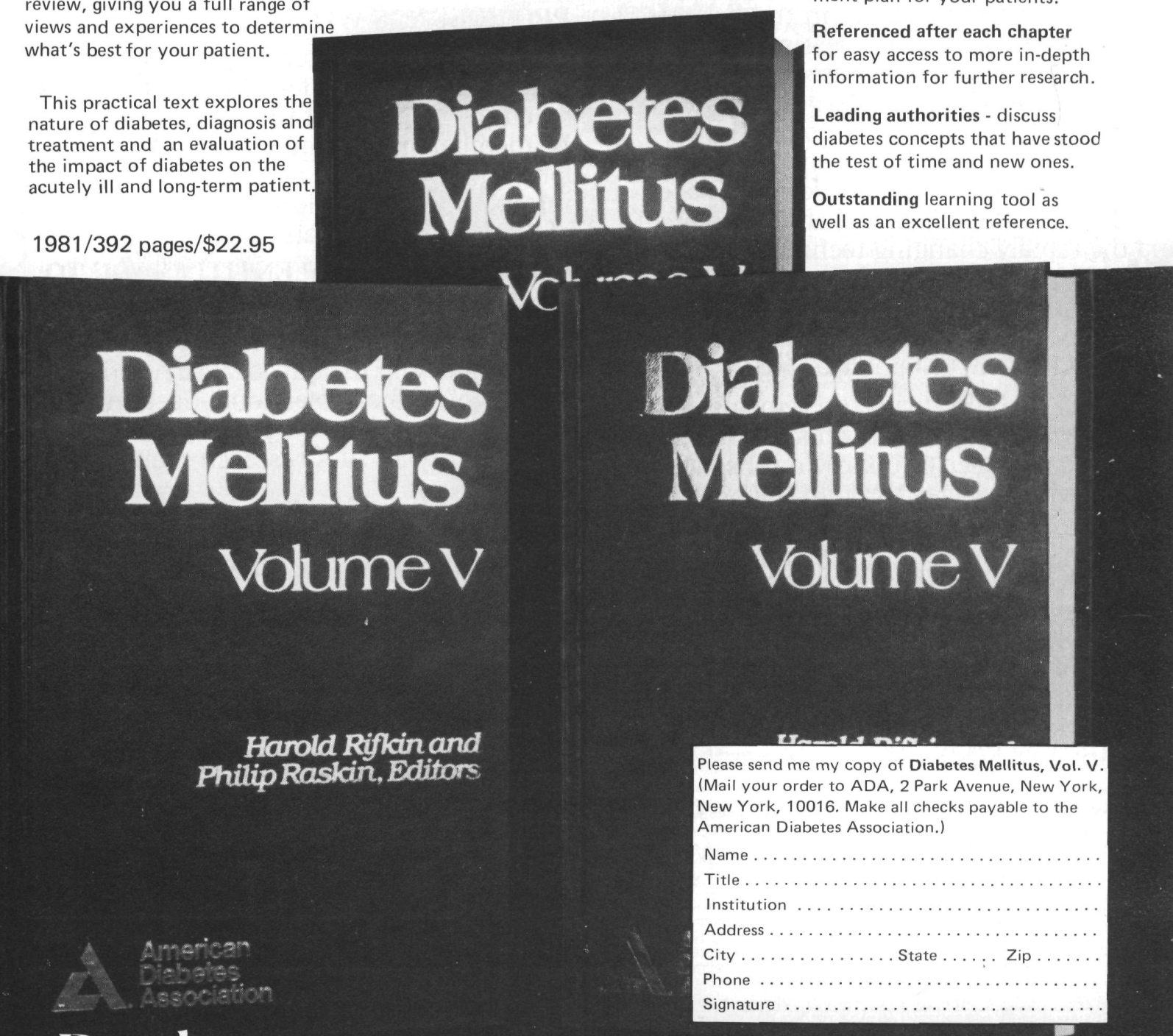

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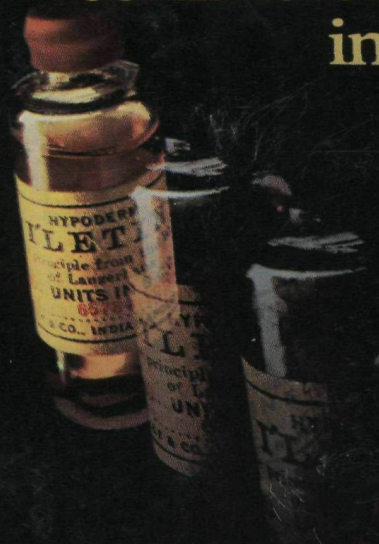
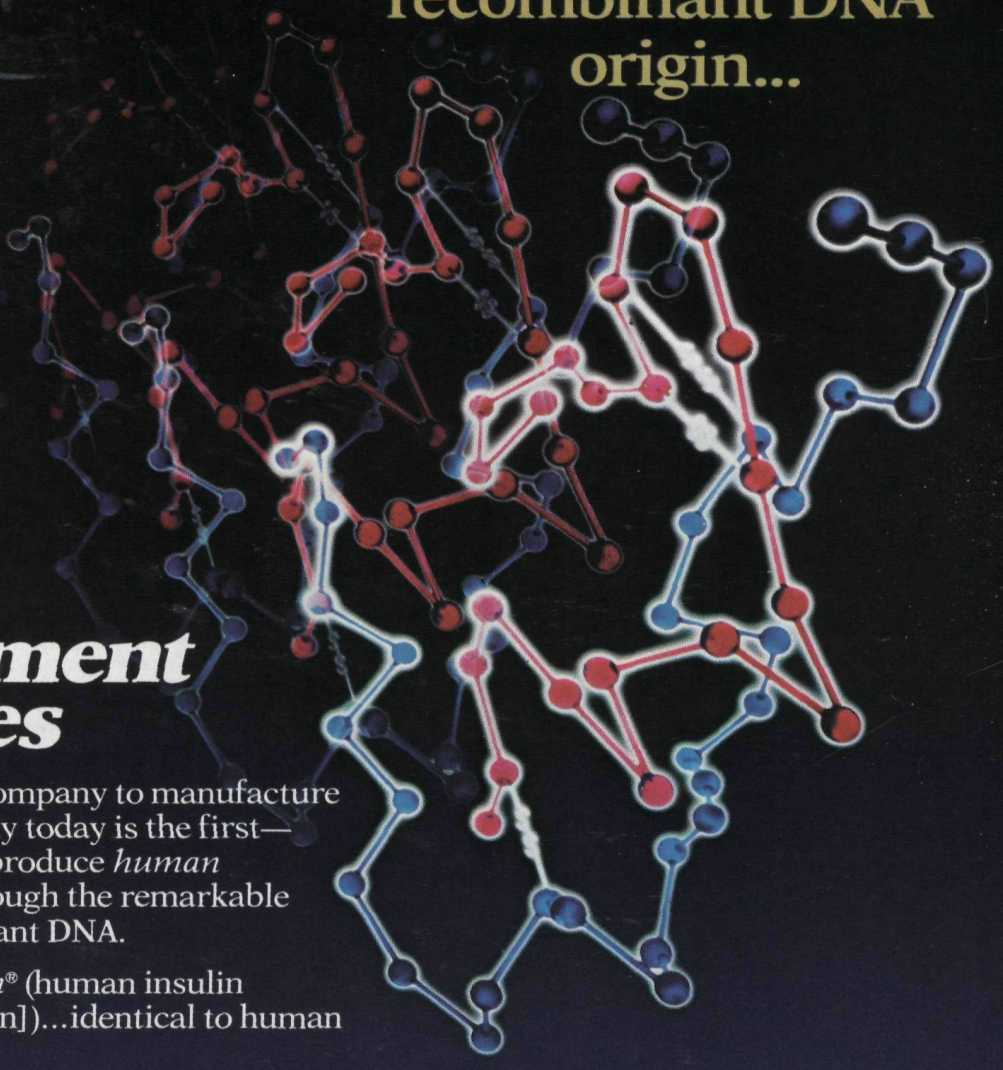
From the first commercially produced insulin...



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



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