THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

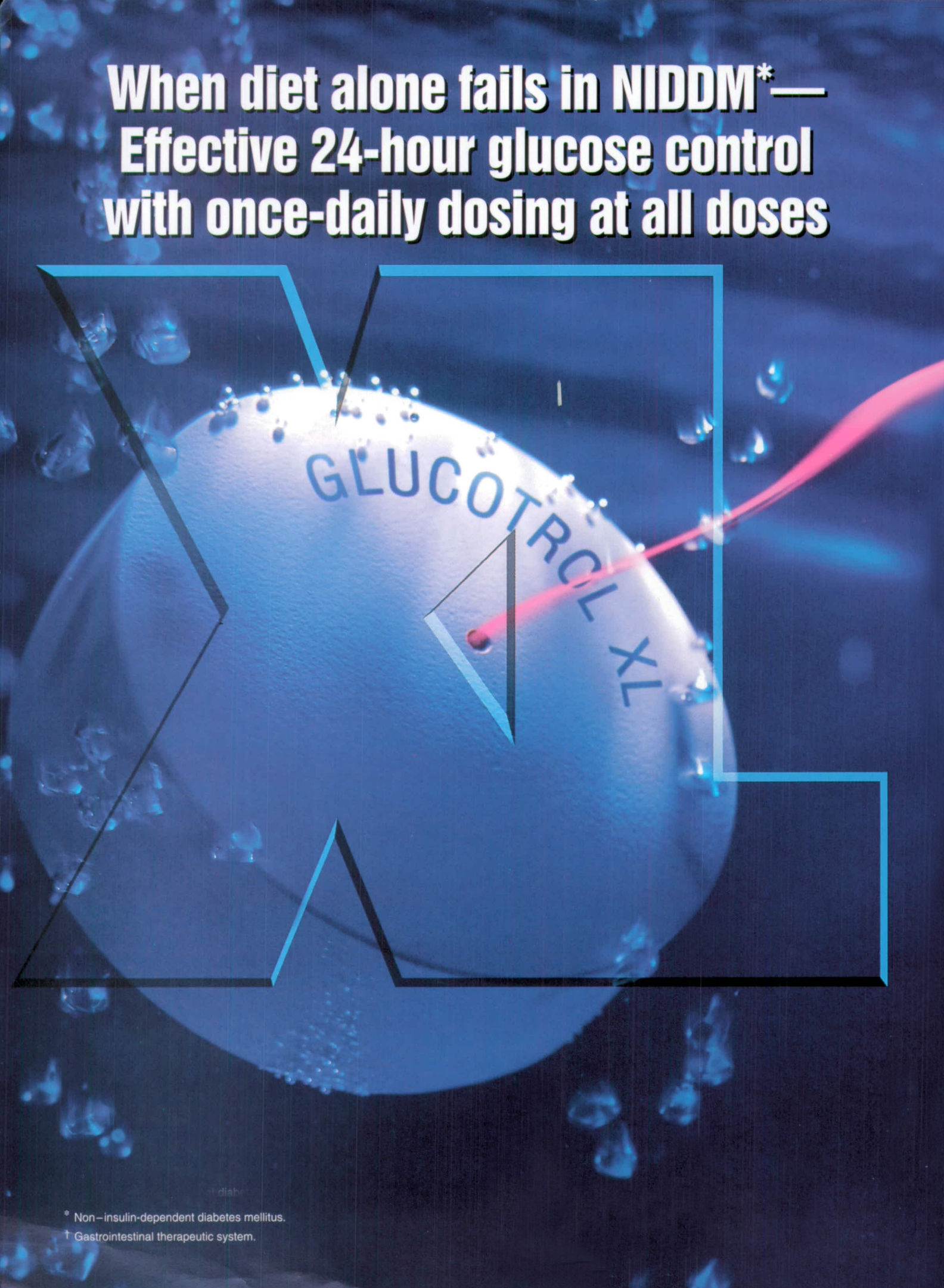
VOLUME 18 NUMBER 10

Diabetes Care

OCTOBER 1995

American Diabetes Association.

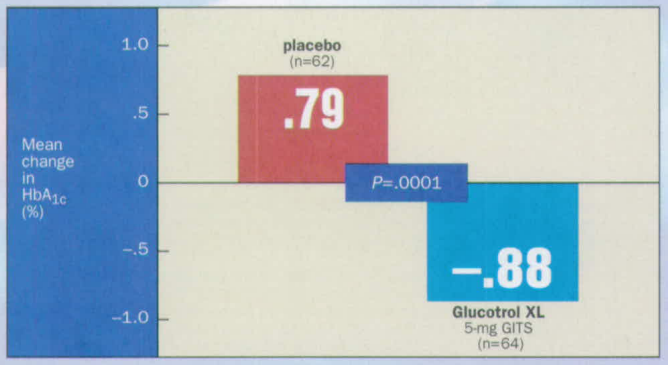
ISSN 0149-5992



* Non–insulin-dependent diabetes mellitus.

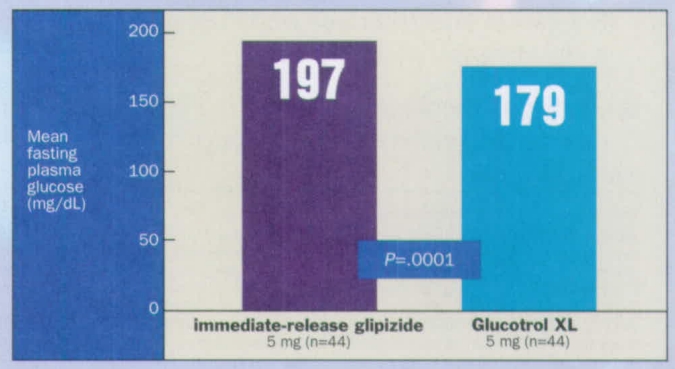
† Gastrointestinal therapeutic system.

Significant decrease in glycosylated hemoglobin (HbA_{1c}) vs placebo[1]



A pooled analysis of two16-week, multicenter, randomized, double-blind, placebo-controlled, fixed-dose studies. After a 1-week washout from current sulfonylurea therapy, or diet failures, patients received 3 weeks of placebo. Following a 4-week titration period in a fixed, double-blind regimen, patients were treated with the assigned dose for 8 weeks.[1]

Significantly lower fasting plasma glucose (FPG) levels and equivalent HbA_{1c} concentrations compared with immediate-release glipizide[1]



Glucotrol XL™ (glipizide) extended release tablets and immediate-release glipizide were compared in a 16-week, multicenter, open-label, crossover study. The data represent the final FPG levels after 8 weeks of each treatment.[1]

Glucotrol XL is well tolerated[1]

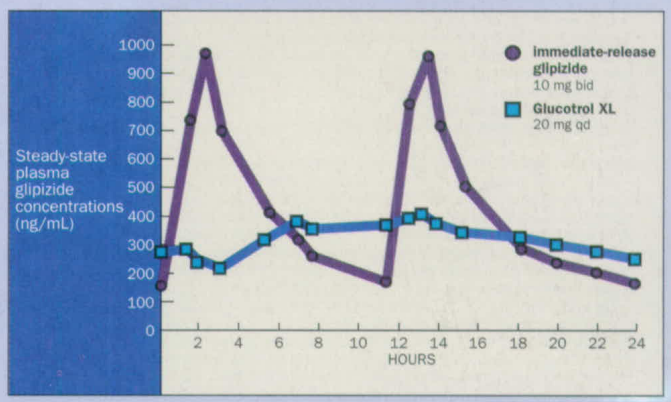
Adverse experiences reported with an incidence of 3% or more[1]

	placebo (%) (n=69)	Glucotrol XL (%) (n=278)
Asthenia	13.0	10.1
Headache	8.7	8.6
Dizziness	5.8	6.8
Diarrhea	0.0	5.4†
Nervousness	2.9	3.6
Tremor	0.0	3.6
Flatulence	1.4	3.2

†Only diarrhea was statistically significant vs placebo.

Incidence of hypoglycemia in 580 patients, who received Glucotrol XL in doses ranging from 5 mg to 60 mg, was 3.4%; only 2.6% of patients discontinued due to hypoglycemia. None of the patients required hospitalization. In the controversial UGDP study, there have been reports of increased cardiovascular risk associated with hypoglycemic therapy.[1]

Glucotrol XL maintains consistent drug levels throughout the day and night[1]



Glucotrol XL 20 mg qd or immediate-release glipizide 10 mg bid were studied in a 5-day, open, randomized, multiple-dose, two-way, crossover study of 20 male patients with NIDDM. Mean glipizide concentration-time profiles on day 5 are shown.[1]

When diet alone fails in NIDDM...

ONCE DAILY **Glucotrol XL**™

(glipizide) extended release

Tablets 5 mg and 10 mg GITS†

As with all sulfonylureas, hypoglycemia may occur.

Please see brief summary of prescribing information on last page.

When diet alone fails in NIDDM...

ONCE DAILY Glucotrol XL™

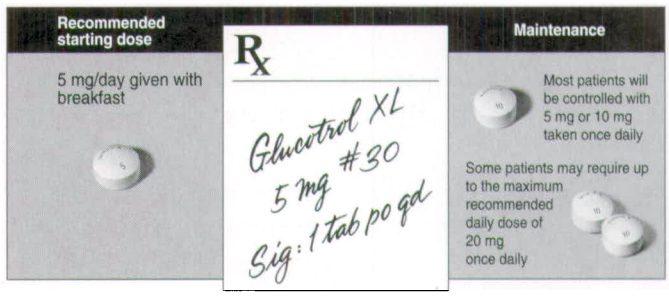
(glipizide) extended release

Tablets 5 mg and 10 mg GITS

- No need to dose 30 minutes before a meal
- Optimal patient care requires careful titration to the lowest effective dose when using all oral sulfonylureas
- Continued monitoring of HbA_{1c} or FPG levels is recommended throughout therapy

Reference: 1. Data on file.

Flexible dosing schedule



Brief Summary of Prescribing Information

INDICATIONS AND USAGE: GLUCOTROL XL 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.

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

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of *oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality* as compared to treatment with diet alone or diet plus insulin.

As with any other non-deformable material, caution should be used when administering GLUCOTROL XL Extended Release Tablets in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of another drug in this non-deformable sustained release formulation.

PRECAUTIONS: Renal and Hepatic Disease: The pharmacokinetics and/or pharmacodynamics of glipizide may be affected in patients with impaired renal or hepatic function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted.

GI Disease: Markedly reduced GI retention times of the GLUCOTROL XL Extended Release Tablets may influence the pharmacokinetic profile and hence the clinical efficacy of the drug.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Renal or hepatic insufficiency may affect the disposition of glipizide 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 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 glipizide and administer insulin. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

Laboratory Tests: Blood and urine glucose should be monitored periodically. Measurement of hemoglobin A_{1c} may be useful.

Information for Patients: Patients should be informed that GLUCOTROL XL Extended Release Tablets should be swallowed whole. Patients should not chew, divide or crush tablets. Patients should not be concerned if they occasionally notice in their stool something that looks like a tablet. In the GLUCOTROL XL Extended Release Tablet, the medication is contained within a nonabsorbable shell that has been specially designed to slowly release the drug so the body can absorb it. When this process is completed, the empty tablet is eliminated from the body.

Patients should be informed of the potential risks and advantages of GLUCOTROL XL 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 also should be explained.

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. In vitro binding studies with human serum proteins indicate that glipizide 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 glipizide 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.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. The effect of concomitant administration of Diflucan® (fluconazole) and Glucotrol® has been demonstrated in a placebo-controlled crossover study in normal volunteers. All subjects received Glucotrol alone and following treatment with 100 mg of Diflucan® as a single daily oral dose for 7 days. The mean percentage increase in the Glucotrol AUC after fluconazole administration was 56.9% (range: 35 to 81%).

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: 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 glipizide. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well controlled studies in pregnant women. Glipizide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 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 glipizide 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 glipizide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. A decision should be made whether to discontinue nursing or to discontinue the drug. 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.

Geriatric Use: Of the total number of patients in clinical studies of GLUCOTROL XL, 33 percent were 65 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some individuals cannot be ruled out. Approximately 1-2 days longer were required to reach steady state in the elderly. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: In U.S. controlled studies the frequency of serious adverse experiences reported was very low and causal relationship has not been established. The 580 patients from 31 to 87 years of age who received GLUCOTROL XL Extended Release Tablets in doses from 5 mg to 60 mg in both controlled and open trials were included in the evaluation of adverse experiences. All adverse experiences reported were tabulated independently of their possible causal relation to medication.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

In double-blind, placebo-controlled studies the adverse experiences reported with an incidence of 3% or more in GLUCOTROL XL-treated patients (N=278) and placebo-treated patients (N=69), respectively, include: Asthenia - 10.1% and 13.0%; Headache - 8.6% and 8.7%; Dizziness - 6.8% and 5.8%; Nervousness - 3.6% and 2.9%; Tremor - 3.6% and 0.0%; Diarrhea - 5.4% and 0.0%; Flatulence - 3.2% and 1.4%.

The following adverse experiences occurred with an incidence of less than 3% in GLUCOTROL XL-treated patients: Body as a whole - pain; Nervous system - insomnia, paresthesia, anxiety, depression and hypesthesia; Gastrointestinal - nausea, dyspepsia, constipation and vomiting; Metabolic - hypoglycemia; Musculoskeletal - arthalgia, leg cramps and myalgia; Cardiovascular - syncope; Skin - sweating and pruritus; Respiratory - rhinitis; Special senses - blurred vision; Urogenital - polyuria.

Other adverse experiences occurred with an incidence of less than 1% in GLUCOTROL XL-treated patients: Body as a whole - chills; Nervous system - hypertonia, confusion, vertigo, somnolence, gait abnormality and decreased libido; Gastrointestinal - anorexia and trace blood in stool; Metabolic - thirst and edema; Cardiovascular - arrhythmia, migraine, flushing and hypertension; Skin - rash and urticaria; Respiratory - pharyngitis and dyspnea; Special senses - pain in the eye, conjunctivitis and retinal hemorrhage; Urogenital - dysuria.

There have been rare reports of gastrointestinal irritation and gastrointestinal bleeding with use of another drug in this non-deformable sustained release formulation, although causal relationship to the drug is uncertain.

The following are adverse experiences reported with immediate release glipizide and other sulfonylureas, but have not been observed with GLUCOTROL XL:

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, glipizide pretreatment did not cause an accumulation of acetaldehyde after ethanol administration. Clinical experience to date has shown that glipizide has an extremely low incidence of disulfiram-like alcohol reactions.

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

OVERDOSAGE: Overdosage 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 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 glipizide from plasma may be prolonged in persons with liver disease. Because of the extensive protein binding of glipizide, dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION: There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOTROL XL Extended Release Tablet or any other hypoglycemic agent. In general, GLUCOTROL XL should be given with breakfast.

Recommended Dosing: The recommended starting dose of GLUCOTROL XL is 5 mg per day, given with breakfast. The recommended dose for geriatric patients is also 5 mg per day.

Dosage adjustment should be based on laboratory measures of glycemic control. While fasting blood glucose levels generally reach steady state following initiation or change in GLUCOTROL XL dosage, a single fasting glucose determination may not accurately reflect the response to therapy. In most cases, hemoglobin A_{1c} level measured at three month intervals is the preferred means of monitoring response to therapy.

Hemoglobin A_{1c} should be measured as GLUCOTROL XL therapy is initiated at the 5 mg dose and repeated approximately three months later. If the result of this test suggests that glycemic control over the preceding three months was inadequate, the GLUCOTROL XL dose may be increased to 10 mg. Subsequent dosage adjustments should be made on the basis of hemoglobin A_{1c} levels measured at three month intervals. If no improvement is seen after three months of therapy with a higher dose, the previous dose should be resumed. Decisions which utilize fasting blood glucose to adjust GLUCOTROL XL therapy should be based on at least two or more similar, consecutive values obtained seven days or more after the previous dose adjustment.

Most patients will be controlled with 5 mg or 10 mg taken once daily. However, some patients may require up to the maximum recommended daily dose of 20 mg. While the glycemic control of selected patients may improve with doses which exceed 10 mg, clinical studies conducted to date have not demonstrated an additional group average reduction of hemoglobin A_{1c} beyond what was achieved with the 10 mg dose.

More detailed information available on request.

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

VOLUME 18 NUMBER 10

Diabetes Care

Diabetes Care is a journal for the health-care practitioner that is intended to increase knowledge, stimulate research, and promote better management of people with diabetes mellitus. To achieve these goals, the journal publishes original articles on human studies in the areas of epidemiology, clinical trials, behavioral medicine, nutrition, education, health-care delivery, medical economics, and clinical care. The journal also publishes clinically relevant review articles, clinical observations, letters to the editor, and public health/medical news or points of view. Topics covered are of interest to clinically oriented physicians, researchers, epidemiologists, psychologists, diabetes educators, and other professionals.

All manuscripts and other editorial correspondence should be sent by first class mail to Allan L. Drash, MD, Editor, *Diabetes Care*, Children's Hospital, Rangos Research Center, 3705 Fifth Avenue, Pittsburgh, PA 15213; (412) 692-5851.

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

Manuscripts should be prepared in accord with the requirements specified in the document "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," *New England Journal of Medicine* 324:424–428, 1991. "Instructions for Authors" containing specifications for manuscript preparation appears in the January and July issues.

Diabetes Care (ISSN 0149-5992) is published monthly by the American Diabetes Association, Inc., 1660 Duke Street, Alexandria, VA 22314. Individual subscription rates are $100 in the U.S., Canada, and Mexico (for Canada add 7% GST) and $155 for all other countries. Institutional rates are $150 in the U.S., Canada, and Mexico (for Canada add 7% GST) and $205 in all other countries. Professional membership includes $75 designated for *Diabetes Care*. Single issues are $11 in the U.S., Canada, and Mexico (Canada add 7% GST) and $26.00 in all other countries. Second class postage paid at Alexandria, VA 22314, and at additional mailing offices. POSTMASTER: Send change of address to *Diabetes Care*, American Diabetes Association, Inc., Journal Subscriptions, Dept. 0028, Washington, DC 20073-0028.

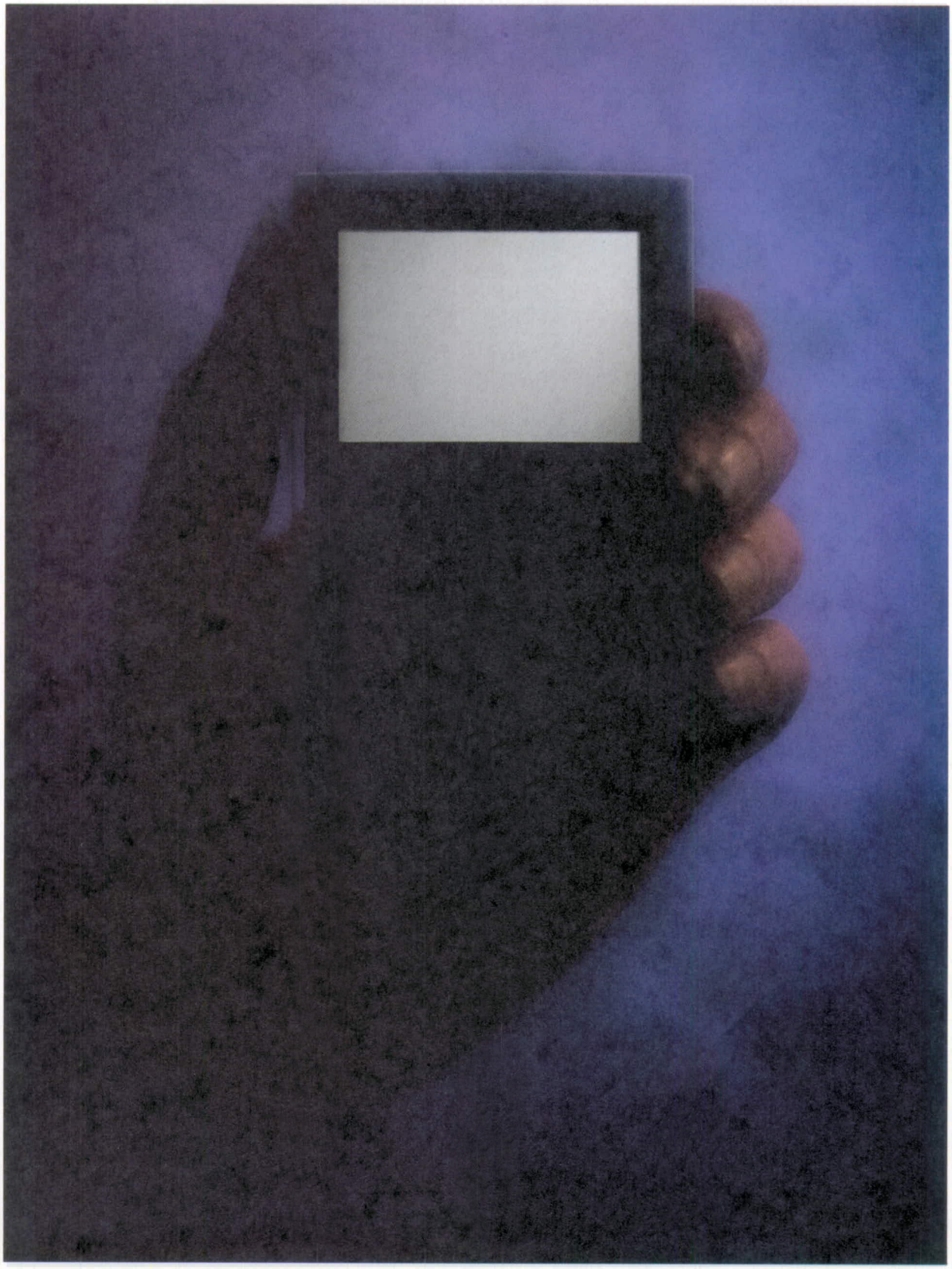
Diabetes Care is listed in Science Citation Index, Current Contents/Life Sciences, Current Contents/Clinical Medicine, SCISEARCH, *EMBASE*, ISI/BIOMED databases, and Automatic Subject Citation Alert. *Diabetes Care* is available online on BRS Colleague. For more information call 800-955-0906. It is also available in machine-readable format from University Microfilms International. *Diabetes Care* is printed on acid-free paper starting with Vol. 11(1), 1988.

The mission of the American Diabetes Association is to prevent and cure diabetes and to improve the lives of all people affected by diabetes.

American Diabetes Association.
ISSN 0149-5992
PRINTED IN THE USA.

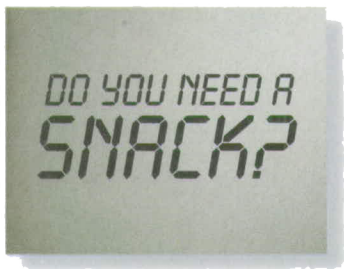
OCTOBER AUTHOR INDEX
(VOLUME 18, NUMBER 10)

"Will you please make a blood glucose monitoring system with..."

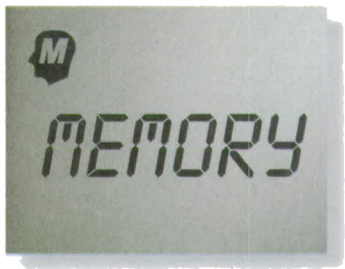


"...a bolder, easier-to-read display."

"...on-screen prompts to simplify learning."

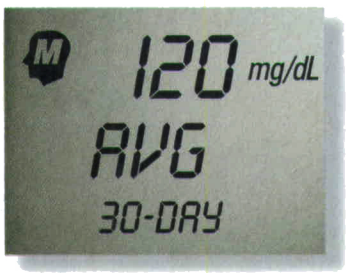


"...easier access to the memory features."

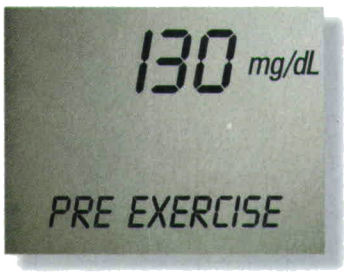


You spoke, and we listened. Introducing the new ONE TOUCH® Profile™ Diabetes Tracking System.

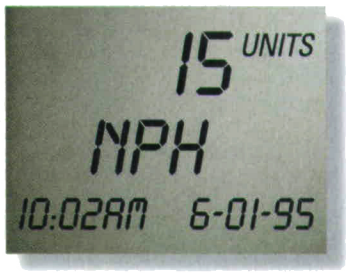
"...a variety of test result averages."



"...a more flexible way to flag test results."



"...a way to record insulin types and dosages."



PRESS POWER, INSERT STRIP.

APPLY SAMPLE. NO WIPING. NO TIMING.

ACCURATE RESULTS IN 45 SECONDS.

You told us what your patients need – features to help see their complete blood glucose profile. The new ONE TOUCH® Profile™ System gives instant overviews with 14-day and 30-day test averages. It helps spot trends by flagging test results with activities. You can even get software that will let you transfer the meter's memory into a personal computer.

And best of all, it's a ONE TOUCH® Brand – the brand most recommended by physicians and diabetes educators. It comes from LifeScan, a Johnson & Johnson company, along with a 30-day, money-back guarantee, a 5-year warranty and 24-hour, toll-free support for both you and your patients.

Call 1 800 524-7226 to find out more. You asked for a simple, complete diabetes tracking system to help your patients. We put one at their fingertips.

For diabetes and life.

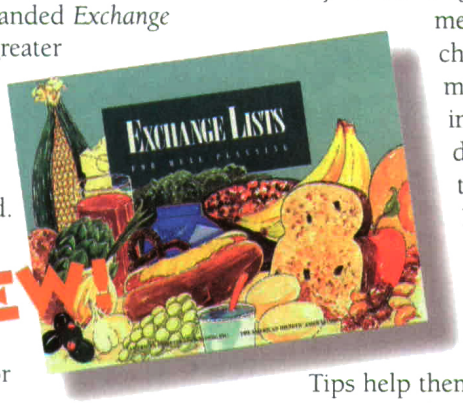
LIFESCAN INC.

a Johnson & Johnson company

New Tools Increase Meal Planning Flexibility

Exchange Lists for Meal Planning

A collaborative effort between the American Diabetes Association and the American Dietetic Association, the revised and expanded *Exchange Lists* offer patients greater meal planning flexibility than ever before.



The new lists have been reordered. Foods are now grouped into three categories based on their major nutrient contents. They've also been expanded to include new products on the market, such as reduced fat or fat-free versions of foods, as well as vegetarian alternatives to meat products. And the combination foods list now includes fast foods.

The revised *Exchange Lists* reflect the 1994 ADA Nutrition Recommendations emphasis on the amount of carbohydrate consumed rather than the type of carbohydrate. This gives patients greater flexibility in choosing their foods at each meal. They can now interchange fruit, starch, and milk lists. They can even include "other carbohydrates", such as cake, into their overall meal plan. Nutrition Tips with each list give patients an overview of the nutrient content of those foods, while Selection Tips help them purchase the correct quantities of foods and prepare them in healthful ways.

	Nonmember	Member
Single copy #CELMPS	*$1.50*	*$1.20*
Pkg of 25 #CELMP2	*$37.50*	*$30.00*

Bulk Pricing (same for members and nonmembers)

5 - 20	*pkgs of 25*	*$28.25 each*
21 - 40	*pkgs of 25*	*$26.25 each*
41+	*pkgs of 25*	*$22.50 each*

NEW!

The First Step in Diabetes Meal Planning

Also developed jointly by the American Diabetes Association and the American Dietetic Association, this colorful tri-fold brochure provides your patients with basic diabetes nutrition guidelines. It opens to an 11" x 18" poster depicting a diabetes food guide pyramid. Written on a very basic level for easy comprehension, this informative pamphlet is ideal for newly diagnosed patients, especially if they are not able to meet with a dietitian right away. Sold in packages of 25. #MODFSP

Nonmember: $9.00; Member: $7.20

To order, call 1-800/ADA-ORDER or send in the coupon below:

What's new with the Exchange Lists?

- **Carbohydrate Group:** patients can now interchange fruit, starch, and milk lists and can incorporate "other carbohydrates" such as pie or frozen yogurt into their meal plans.
- **Meat and Meat Substitutes Group:** includes the new Very Lean Meat list of foods containing 1 gram or less of fat and no more than 35 calories per serving.
- **Fat Group:** now has 3 lists - monounsaturated, polyunsaturated, and saturated fats; encourages use of foods containing monounsaturated fat.

❑ YES! Please send me the books I've listed, and include a free catalog.
❑ NO. I'm not ordering right now, but please send me a free catalog.

Item #	Item Name	Qty	Unit Price	Total

Shipping & Handling	
up to $30.00	add $3.00
$30.01–$50.00	add $4.00
over $50.00	add 8%

Publications Subtotal..... $_____
VA Residents add 4.5% tax..... $_____
Shipping & Handling (see chart) $_____
Total Due..... $_____

Allow 2-3 weeks for shipment. Add $3 to shipping & handling for each extra shipping address. Add $15 for each overseas address. Prices subject to change without notice.

Ship To

First Name _____ Middle Initial _____ Last Name _____

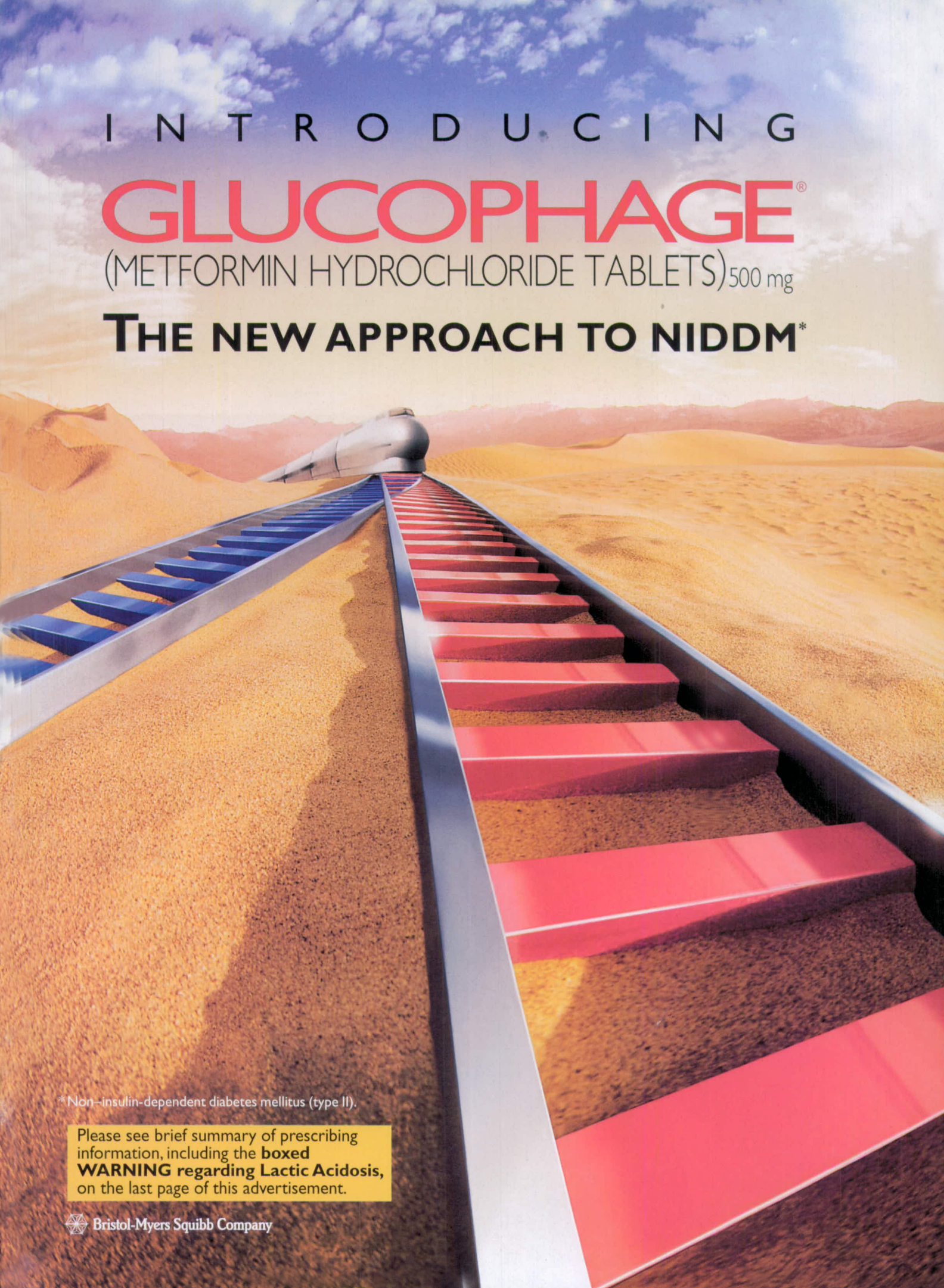
Address _____

City/State/Zip _____ P26C85

❑ Payment enclosed (check or money order)
Charge my: ❑ VISA ❑ MC ❑ AMEX
Account Number: _____
Signature: _____ Exp. Date: ___/___

Mail to: American Diabetes Association
Order Fulfillment Department
P.O. Box 930850
Atlanta, GA 31193-0850

American Diabetes Association.


INTRODUCING
GLUCOPHAGE®
(METFORMIN HYDROCHLORIDE TABLETS) 500 mg
THE NEW APPROACH TO NIDDM*
* Non–insulin-dependent diabetes mellitus (type II).
Please see brief summary of prescribing information, including the **boxed WARNING regarding Lactic Acidosis,** on the last page of this advertisement.
Bristol-Myers Squibb Company

THE NEW *NON*-SULFONYLUREA APPROACH TO NIDDM

BYPASSES THE PANCREAS WITH

GLUCOPHAGE lowers blood glucose levels without stimulating insulin secretion.[1]

No effect on pancreatic beta cells or insulin secretion.[1]

Does not produce hypoglycemia.[1]

GLUCOPHAGE is highly effective first-line drug therapy.[2]

Significantly decreases fasting plasma glucose (FPG) when used as an adjunct to diet.[2]

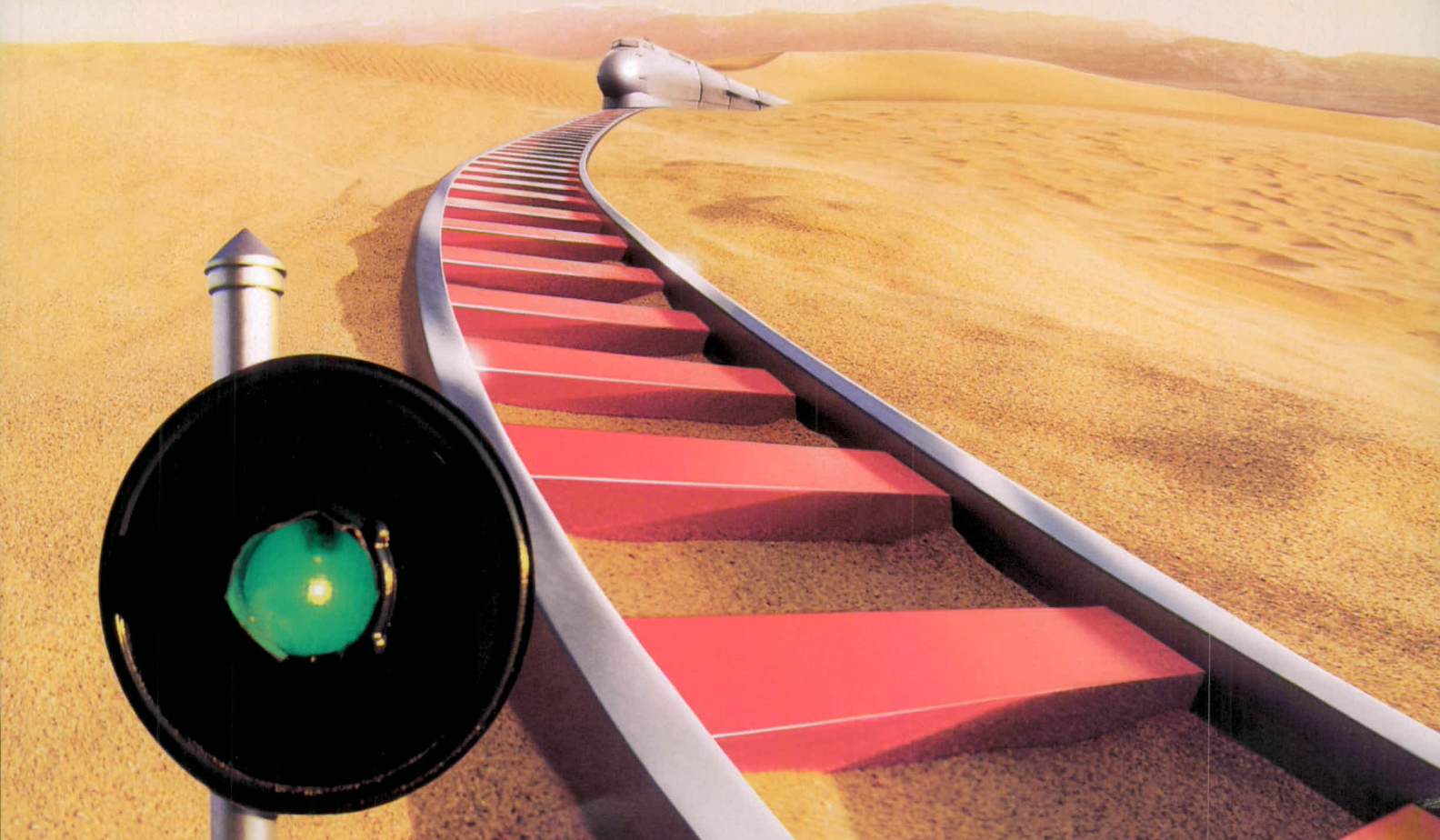
Mean difference in FPG compared to placebo

GLUCOPHAGE vs placebo

P=0.001

-59 mg/dL

Study 1: Results of a double-blind, placebo-controlled, multicenter trial over 29 weeks. 286 randomized NIDDM patients: GLUCOPHAGE, n=141; placebo, n=145. Average dosage of GLUCOPHAGE was 1,980 mg/day.[2]



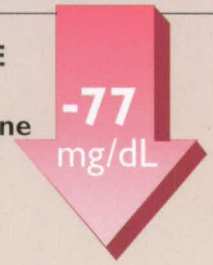
DIRECT ANTIHYPERGLYCEMIC ACTION.

GLUCOPHAGE is synergistic in combination.[2]

Combining GLUCOPHAGE and a sulfonylurea with diet lowers FPG significantly more than monotherapy.[2]

Mean difference in FPG compared to monotherapy

GLUCOPHAGE plus glyburide vs glyburide alone



P=0.001

Study 2: Results of a double-blind, placebo-controlled, parallel-group, multicenter trial comparing GLUCOPHAGE (n=210), glyburide (n=209), and the combination (n=213) over 29 weeks. 632 randomized NIDDM patients in whom glyburide monotherapy (20 mg/day) had failed to provide adequate control. Average dosage of GLUCOPHAGE was 2,050 mg/day as monotherapy and 1,894 mg/day in combination.[2]

GLUCOPHAGE produces modest improvements in key lipids.[1]

Significantly reduces total cholesterol, LDL cholesterol, and triglycerides ($P<0.05$), and has a neutral effect on HDL cholesterol.[1,2]

Improvement noted particularly when baseline lipid levels were elevated.[1]

GLUCOPHAGE can help NIDDM patients keep their weight under control while lowering blood glucose.[1]

In contrast to sulfonylureas, body weight of individuals on GLUCOPHAGE tends to remain stable or decrease.[1]

NEW

WITH DIET—ALONE OR WITH A SULFONYLUREA

GLUCOPHAGE®

(METFORMIN HYDROCHLORIDE TABLETS) 500 mg

THE NEW APPROACH TO NIDDM

Please see brief summary of prescribing information, including the **boxed WARNING regarding Lactic Acidosis,** on the last page of this advertisement.

THE NEW *NON*-SULFONYLUREA APPROACH TO NIDDM

PROVIDES ESTABLISHED SAFETY AND OFFERS BID DOSING.

Safety established in over 3 million patient-years of experience.[3]

Mild and transient GI side effects are most common.[1]

Diarrhea, nausea, vomiting, bloating, or flatulence may occur, especially during initiation of GLUCOPHAGE

- approximately 30% more frequent than with placebo[1]
- approximately 4% of patients discontinue therapy due to GI reactions.[1]

Rare occurrence of lactic acidosis, a serious condition.

Approximately 0.03 cases per 1,000 patient-years reported worldwide[1]

- if cases occur, up to half may be fatal
- seen primarily in patients with renal insufficiency
- Patient Package Insert lists symptoms to be discussed with patients.

The UGDP study suggested increased cardiovascular risk with oral antidiabetics.

Appropriate patient selection is key.[1]

Contraindicated in patients with renal disease or renal dysfunction and in patients with metabolic acidosis.

Temporarily withhold in patients receiving iodinated contrast materials for radiologic studies.

Avoid in patients with impaired hepatic function or excessive alcohol intake (acute or chronic).

Not recommended for children or pregnant women.

Recommended starting dosage: 500 mg bid with meals.[1]

Increase dosage by one 500 mg tablet each week.

Minimize GI reactions by slow titration and administration with food

- occasionally, temporary dose reduction may be useful.

Individualize dosage based on effectiveness and tolerance, up to a maximum of 2500 mg administered on a tid schedule.

NEW

WITH DIET—ALONE OR WITH A SULFONYLUREA

GLUCOPHAGE®

(METFORMIN HYDROCHLORIDE TABLETS) 500 mg

THE NEW APPROACH TO NIDDM

References: 1. GLUCOPHAGE Package Insert. **2.** Data on file, Bristol-Myers Squibb Company. **3.** Sirtori CR, Pasik C: Re-evaluation of a biguanide, metformin: mechanism of action and tolerability. *Pharmacol Res* 30(3):187-228, 1994.

Please see brief summary of prescribing information, including the **boxed WARNING regarding Lactic Acidosis,** on the last page of this advertisement.

GLUCOPHAGE® (METFORMIN HYDROCHLORIDE TABLETS) 500 mg

CONTRAINDICATIONS: GLUCOPHAGE is contraindicated in patients with: **1.** Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS and PRECAUTIONS). **2.** GLUCOPHAGE should be temporarily withheld in patients undergoing radiologic studies involving parenteral administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. (See also PRECAUTIONS). **3.** Known hypersensitivity to metformin hydrochloride. **4.** Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

WARNINGS: Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with GLUCOPHAGE; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1,000 patient-years, with approximately 0.015 fatal cases/1,000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking GLUCOPHAGE and by use of the minimum effective dose of GLUCOPHAGE. In addition, GLUCOPHAGE should be promptly withheld in the presence of any condition associated with hypoxemia or dehydration. Because impaired hepatic function may significantly limit the ability to clear lactate, GLUCOPHAGE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking GLUCOPHAGE, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, GLUCOPHAGE should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see also PRECAUTIONS). The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). GLUCOPHAGE should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of GLUCOPHAGE, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking GLUCOPHAGE do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling. (See also PRECAUTIONS.) Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking GLUCOPHAGE, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See also CONTRAINDICATIONS and PRECAUTIONS).

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral antidiabetic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.

PRECAUTIONS: General: ***Monitoring of renal function*** — GLUCOPHAGE is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive GLUCOPHAGE. In patients with advanced age, GLUCOPHAGE should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, renal function should be monitored regularly and, generally, GLUCOPHAGE should not be titrated to the maximum dose (see DOSAGE AND ADMINISTRATION). Before initiation of GLUCOPHAGE therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and GLUCOPHAGE discontinued if evidence of renal impairment is present. — ***Use of concomitant medications that may affect renal function or metformin disposition*** —Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of GLUCOPHAGE, such as cationic drugs that are eliminated by renal tubular secretion (See Drug Interactions), should be used with caution. — ***Radiologic studies involving the use of iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and scans with contrast materials)*** — Parenteral contrast studies with iodinated materials can lead to acute renal failure and have been associated with lactic acidosis in patients receiving GLUCOPHAGE (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, GLUCOPHAGE should be withheld for at least 48 hours prior to, and 48 hours subsequent to, the procedure and reinstituted only after renal function has been re-evaluated and found to be normal. — ***Hypoxic states*** — Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on GLUCOPHAGE therapy, the drug should be promptly discontinued. — ***Surgical procedures*** — GLUCOPHAGE therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal. — ***Alcohol intake*** — Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving GLUCOPHAGE. — ***Impaired hepatic function*** — Since impaired hepatic function has been associated with some cases of lactic acidosis, GLUCOPHAGE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. — ***Vitamin B_{12} levels*** — A decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, is observed in approximately 7% of patients receiving GLUCOPHAGE in controlled clinical trials of 29 weeks duration. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of GLUCOPHAGE or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on GLUCOPHAGE and any apparent abnormalities should be appropriately investigated and managed (see Laboratory Tests). Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at two- to three-year intervals may be useful. — ***Change in clinical status of previously controlled diabetic*** — A diabetic patient previously well controlled on GLUCOPHAGE who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and metformin levels. If acidosis of either form occurs, GLUCOPHAGE must be stopped immediately and other appropriate corrective measures initiated (see also WARNINGS). — ***Hypoglycemia*** — Hypoglycemia does not occur in patients receiving GLUCOPHAGE alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas) or ethanol. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs. — ***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 temporary loss of glycemic control may occur. At such times, it may be necessary to withhold GLUCOPHAGE and temporarily administer insulin. GLUCOPHAGE may be reinstituted after the acute episode is resolved. The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with GLUCOPHAGE or sulfonylurea monotherapy, combined therapy with GLUCOPHAGE and sulfonylurea may result in a response. Should secondary failure occur with combined GLUCOPHAGE/sulfonylurea therapy, it may be necessary to initiate insulin therapy. — **Information for Patients:** Patients should be informed of the potential risks and advantages of GLUCOPHAGE and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function and hematologic parameters. The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the WARNINGS and PRECAUTIONS sections should be explained to patients. Patients should be advised to discontinue GLUCOPHAGE® (metformin hydrochloride tablets) immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of GLUCOPHAGE, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Patients should be counselled against excessive alcohol intake, either acute or chronic, while receiving GLUCOPHAGE. GLUCOPHAGE alone does not usually cause hypoglycemia, although it may occur when GLUCOPHAGE is used in conjunction with oral sulfonylureas. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients. (See Patient Package Insert.) — **Laboratory Tests:** Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control (see also DOSAGE AND ADMINISTRATION). Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with GLUCOPHAGE therapy, if this is suspected, vitamin B_{12} deficiency should be excluded. — **Drug Interactions:** ***Glyburide*** — In a single-dose interaction study in NIDDM subjects, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain (see DOSAGE AND ADMINISTRATION, Concomitant Glucophage and Oral Sulfonylurea Therapy). — ***Furosemide*** — A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically. — ***Nifedipine*** — A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine. — ***Cationic drugs*** — Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of GLUCOPHAGE and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system. — ***Other*** — Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazide 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 GLUCOPHAGE, the patient should be closely observed to maintain adequate glycemic control. In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies. Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins. — **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately three times the maximum recommended human daily dose on a body surface area basis. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. However, an increased incidence of benign stromal uterine polyps was seen in female rats treated with 900 mg/kg/day. No evidence of a mutagenic potential of metformin was found in the Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes), or *in-vivo* micronuclei formation test (mouse bone marrow). Fertility of male or female rats was unaffected by metformin administration at doses as high as 600 mg/kg/day, or approximately two times the maximum recommended human daily dose on a body surface area basis. — **Pregnancy:** ***Teratogenic effects — Pregnancy Category B.*** Safety in pregnant women has not been established. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, or about two times the maximum recommended human daily dose on a body surface area basis. Determination of fetal concentrations demonstrated a partial placental barrier to metformin. Because animal reproduction studies are not always predictive of human response, any decision to use this drug should be balanced against the benefits and risks. Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, there is a consensus among experts that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. — **Nursing Mothers:** Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers, but caution should be exercised in such patients, and 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. — **Pediatric Use:** Safety and effectiveness in children have not been established. Studies in maturity-onset diabetes of the young (MODY) have not been conducted. — **Geriatric Use:** Controlled clinical studies of GLUCOPHAGE did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. GLUCOPHAGE is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, it should only be used in patients with normal renal function (see CONTRAINDICATIONS, CLINICAL PHARMACOLOGY, Pharmacokinetics). Because aging is associated with reduced renal function, GLUCOPHAGE should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of GLUCOPHAGE (see also DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: Lactic Acidosis: See WARNINGS, PRECAUTIONS and OVERDOSAGE Sections. — **Gastrointestinal Reactions:** Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to GLUCOPHAGE and are approximately 30% more frequent in patients on GLUCOPHAGE monotherapy than in placebo-treated patients, particularly during initiation of GLUCOPHAGE therapy. These symptoms are generally transient and resolve spontaneously during continued treatment. Occasionally, temporary dose reduction may be useful. In controlled trials, GLUCOPHAGE was discontinued due to gastrointestinal reactions in approximately 4% of patients. Because gastrointestinal symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take GLUCOPHAGE with meals (see DOSAGE AND ADMINISTRATION). Because significant diarrhea and/or vomiting may cause dehydration and prerenal azotemia, under such circumstances, GLUCOPHAGE should be temporarily discontinued. For patients who have been stabilized on GLUCOPHAGE, nonspecific gastrointestinal symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis have been excluded. — **Special Senses:** During initiation of GLUCOPHAGE therapy, approximately 3% of patients may complain of an unpleasant or metallic taste, which usually resolves spontaneously. — **Dermatologic Reactions:** The incidence of rash/dermatitis in controlled clinical trials was comparable to placebo for GLUCOPHAGE monotherapy and to sulfonylurea for GLUCOPHAGE/sulfonylurea therapy. — **Hematologic:** (See also PRECAUTIONS). During controlled clinical trials of 29 weeks duration, approximately 9% of patients on GLUCOPHAGE monotherapy and 6% of patients on GLUCOPHAGE/sulfonylurea therapy developed asymptomatic subnormal serum vitamin B_{12} levels; serum folic acid levels did not decrease significantly. However, only five cases of megaloblastic anemia have been reported with metformin administration (none during U.S. clinical studies) and no increased incidence of neuropathy has been observed. Therefore, serum B_{12} levels should be appropriately monitored or periodic parenteral B_{12} supplementation considered.

OVERDOSAGE: Hypoglycemia has not been seen even with ingestion of up to 85 grams of GLUCOPHAGE, although lactic acidosis has occurred in such circumstances (see WARNINGS). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

Consult package insert before prescribing GLUCOPHAGE (metformin hydrochloride tablets). F5-B001A 1/95

GLUCOPHAGE is a registered trademark of LIPHA s.a.

Licensed to Bristol-Myers Squibb Company.

Manufactured by Lipha Pharmaceuticals Ltd., Hitchin, UK.

Distributed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA.

MEDWatch 1-800-332-1088 available to report serious adverse events for any drug.

 F5-K006 Issued: May 1995

The latest weapons in the fight against diabetes.

Call 1-800-254-WALK

You don't need a medical degree to help find a cure for diabetes. Just a sturdy pair of walking shoes.

Walk with us, or sponsor a walker in this year's Walktoberfest. It's the American Diabetes Association's® largest annual event to raise funds for research and to help people with diabetes live better lives.

By taking this important step, you'll be helping to save millions of Americans from the devastating effects of diabetes – blindness, loss of limbs, even death.

So when a neighbor asks, make a pledge. Or better yet, call us and join the walk. Because if we're going to find a cure, we all need to put our best foot forward.

EQUAL® Sweetener Presents

Walktoberfest®

an event of American Diabetes Association®

SATURDAY, SEPTEMBER 30 OR SUNDAY, OCTOBER 1

LUDEN'S · Estee · GuiltFree NONFAT ICE CREAM · People · Cary's SUGAR FREE SYRUP

Treat your patients.

The next time you see your diabetic, diet-restricted patients, give them a treat. Tell them sweet, fruity, delicious, naturally fat-free Sugar Free Jell-O® Gelatin is a free exchange, so they can have it whenever they want. While you're at it, treat your patients to a free Sugar Free Jell-O® Gelatin recipe brochure. To order yours, just call us at **1 800 SAY-JELL-O**.

Dessert is Back!

10 calories per 1/2 cup serving. **Exchange: Free Food Exchange.** Calculations based on Exchange Lists for Meal Planning.

Clinical Education Series Goes Hi-Tech

The ADA Clinical Education Series on CD-ROM

The world's most comprehensive diabetes treatment information can be at your fingertips in seconds with CD-ROM technology! Presenting the first all-in-one database of diabetes treatment information. Includes: *Medical Management of Type I Diabetes; Medical Management of Type II Diabetes; Therapy for Diabetes Mellitus and Related Disorders, 2nd Ed.; Medical Management of Pregnancy Complicated by Diabetes, 2nd Ed.;* plus ADA's *Clinical Practice Recommendations 1995.*

All of these titles are on one compact disc, allowing for quick searches of key terms and phrases across all titles in the database. It also features a "hypertext link" giving you instantaneous browsing between text, references, and illustrations. Best of all, it's easy to install and use. You need no previous familiarity with CD-ROM technology. If you do have questions or need assistance, there's a toll-free line to technical experts who will be happy to help. Works in Windows or Macintosh environment.

System requirements: Macintosh - 68020 or greater processor, System 7.0 or greater, 2MB RAM (4MB recommended); Windows - 386 or 486 processor (486 recommended), Windows 3.1 or greater, 4MB RAM. 1995.

#PCDROM1 • *Nonmember: $225.00; Member: $179.50*

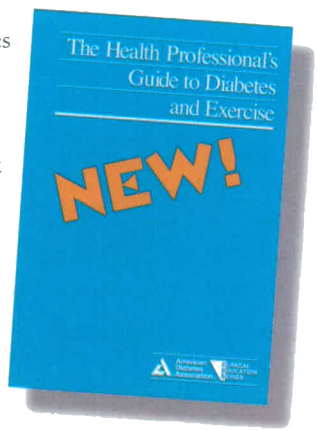
New Titles Give Health Pros Practical Treatment Advice

Intensive Diabetes Management

An all-inclusive "how to" manual on implementing tight diabetes control in your practice. Written by a team of experts with first-hand DCCT experience, this valuable guide provides you with the practical information needed to implement intensive management. Softcover; approximately 112 pages.

Contents: The Team Approach to Intensive Management • Education • Rationale for Intensification • Multiple-Component Insulin Regimens • Monitoring • Nutrition • Psychological Support and Behavioral Issues • Follow-Up and Preventive Care Guidelines • Alternative Insulin Delivery Systems • Complications and Adverse Effects • Resources

#PMIDM • *Nonmember: $37.50; Member: $29.95*



The Health Professional's Guide to Diabetes and Exercise

The first comprehensive guide to prescribing exercise as a therapy in managing diabetes. This valuable book examines the physiological effects of exercise and its metabolic benefits for patients with diabetes. And it covers dietary management and insulin adjustment, as well as behavioral and compliance issues as they relate to the exercise prescription.

The Handbook also delves into special situations such as prescribing exercise for patients with complications, pregnant patients, and older adults. An invaluable resource for anyone treating patients with diabetes! Softcover; approximately 350 pages.

Contents: Basic Considerations • The Treatment Plan • Exercise in Patients with Diabetic Complications • Special Patient Groups • Different Sports: Practical Advice and Experience

#PMHDE • *Nonmember: $49.95; Member: $39.95*

To order, call 1-800/ADA-ORDER or send in the coupon below:

❑ YES! Please send me the books I've listed, and include a free catalog.
❑ NO. I'm not ordering right now, but please send me a free catalog.

Item #	Item Name	Qty	Unit Price	Total

Shipping & Handling	
up to $30.00	add $3.00
$30.01–$50.00	add $4.00
over $50.00	add 8%

Publications Subtotal..... $_____
VA Residents add 4.5% tax..... $_____
Shipping & Handling (see chart) $_____
Total Due..... $_____

Allow 2-3 weeks for shipment. Add $3 to shipping & handling for each extra shipping address. Add $15 for each overseas address. Prices subject to change without notice.

Ship To

First Name _____ Middle Initial _____ Last Name _____

Address _____

City/State/Zip _____ P23C85

❑ Payment enclosed (check or money order)

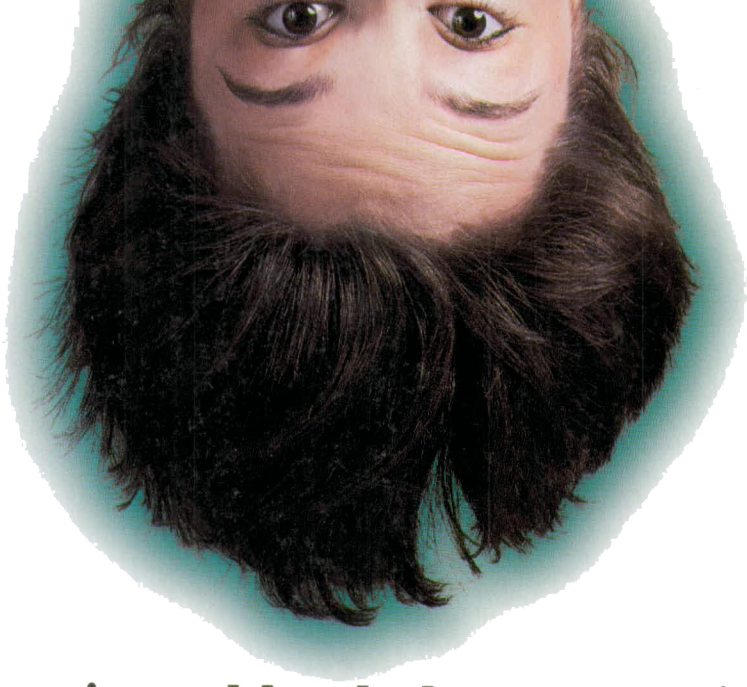
Charge my: ❑ VISA ❑ MC ❑ AMEX

Account Number: _____

Signature: _____ Exp. Date: ___/___

Mail to: American Diabetes Association
Order Fulfillment Department
P.O. Box 930850
Atlanta, GA 31193-0850

American Diabetes Association.



Imagine a blood glucose monitor that actually lets you test like this.

Introducing the NEW Precision Q·I·D™ System. Easy, accurate blood glucose testing. Anytime. Anywhere.

Chances are your patients won't be testing their blood glucose upside down. But they could, with the new Precision Q·I·D hand-held monitor and unique MICROFLO™ test strip — a major improvement in test strip technology from MediSense. **See for yourself.** Now people with diabetes can easily test in a wide range of positions and environments. Easily, accurately, and discreetly, in just 20 seconds. At home, at work, or on the go. The Precision Q·I·D System. It's new. It's easy. And it's available only from MediSense.

Introducing the revolutionary new Precision Q·I·D™ System.

Test 4 Better Control™

For more information on the new Precision Q·I·D System, call MediSense at 1-800-527-3339

National Presenting Sponsor of National Diabetes Month
A Program of the American Diabetes Association

MEDISENSE®

Until there's non-invasive, there's non-intrusive.™

43rd ANNUAL ADVANCED

American Diabetes Association's

43rd Annual Advanced

Postgraduate Course

January 19 - 21, 1996

New York Marriott Marquis Hotel

New York, New York

FRIDAY, JANUARY 19

General Session: Issues in Diabetes Care – Part I

Novel Pharmacological Treatments for NIDDM

Physiologic Insulin Replacement: Meeting The Challenge

Does Exogenous Insulin Cause Macrovascular Disease in NIDDM?

Standardization of the HbA_{1c} Assay

Diabetes Prevention Program: Purpose and Study Design

General Session: Issues in Endocrinology

Management of Hyperthyroidism

Endocrine Disorders and Their Relationship to Sexual Dysfunction

Clinical Utility of Growth Hormone Administration in Adults

Diagnosis and Management of Cushing Syndrome

SATURDAY, JANUARY 20

General Session: Nutrition and Obesity

The Control of Food Intake and Body Weight

The Genetics of Obesity

The Pharmacological Treatment of Obesity

Should We Pay Attention to Micronutrients in the Diet?

Treatment of Eating Disorders in Diabetes

NEW YORK...

POSTGRADUATE COURSE

Concurrent Workshops:

Blood Glucose Awareness Training

Intensive Therapy and Weight Issues in Children and Adolescents

What Are Appropriate Outcome Measures for Diabetes Care and Education?

Recognizing and Treating Depression in Diabetes

Controversies in Gestational Diabetes

Using the New Nutrition Tools in Clinical Practice

Carbohydrate Counting in Diabetes Management

SUNDAY, JANUARY 21

General Session: Issues in Diabetes Care – Part II

Delivery of Diabetes Care in a Managed Care Setting

New Technologies to Measure Blood Glucose

Report of the Workgroup to Revise the Diagnosis and Classification of Diabetes

Female Sexual Dysfunction in Diabetes

Hormonal Replacement Therapy in Postmenopausal Women with Diabetes

Join us in New York City for innovative sessions on the latest in clinical research in areas of interest to all health-care professionals in the field of diabetes. This year's program has been designed to highlight new information and to facilitate discussion on topics and issues related to diabetes treatment and care. Lecture presentations and interactive workshops promise to provide a rewarding educational opportunity for attendees.

Located in the heart of the Theater District in Manhattan, you'll discover the New York Marriott Marquis Hotel. Rising 50 stories above the lights of Broadway, the Marriott Marquis Hotel is just minutes from all that New York has to offer. Step outside to the revitalized Times Square, fabulous shopping, and fine dining on Restaurant Row. Just minutes away you'll find the World Trade Center, the Statue of Liberty and the rest of "the city that never sleeps." From fashion and shopping to culture and dining, New York has something for everyone. The Marriott Marquis Hotel provides the perfect setting for the 43rd Annual Advanced Postgraduate Course.

43rd ANNUAL ADVANCED POSTGRADUATE COURSE

the place to be.

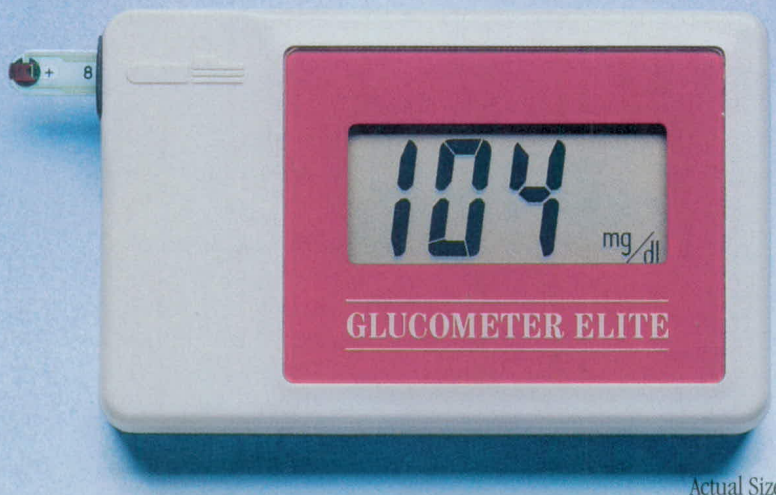
American Diabetes Association.

For more information contact:
Meeting Services Department
1660 Duke Street
Alexandria, VA 22314-3447 USA
Phone: 703/549-1500, ext. 2453
Fax: 703/683-1351

Act Now!!

Recommend the new standard for simplicity.

NOW UP TO $90 OFF
$50 REBATE* + $40 COMPETITIVE TRADE-IN



Actual Size

No buttons...no bother!

With the GLUCOMETER ELITE® Diabetes Care System, there are no buttons to push, and no need to wipe or blot test strips. Your patients just insert the GLUCOMETER ELITE Test Strip to activate the meter, touch blood to the tip of the strip, and read the results in 60 seconds. Even the right amount of blood is determined automatically.

No wonder three out of four people surveyed gave the GLUCOMETER ELITE System an overall rating of "excellent" or "very good." It's the first system for diabetes care that's more than technique-independent. It's virtually technique-free.

The GLUCOMETER ELITE System comes with everything your patients need to start blood glucose testing. For more information, contact your Bayer Corporation (formerly Miles Inc.), Diagnostics Division sales representative, or call toll-free 1-800-445-5901.

*Consumer promotion effective February 1–December 31, 1995.

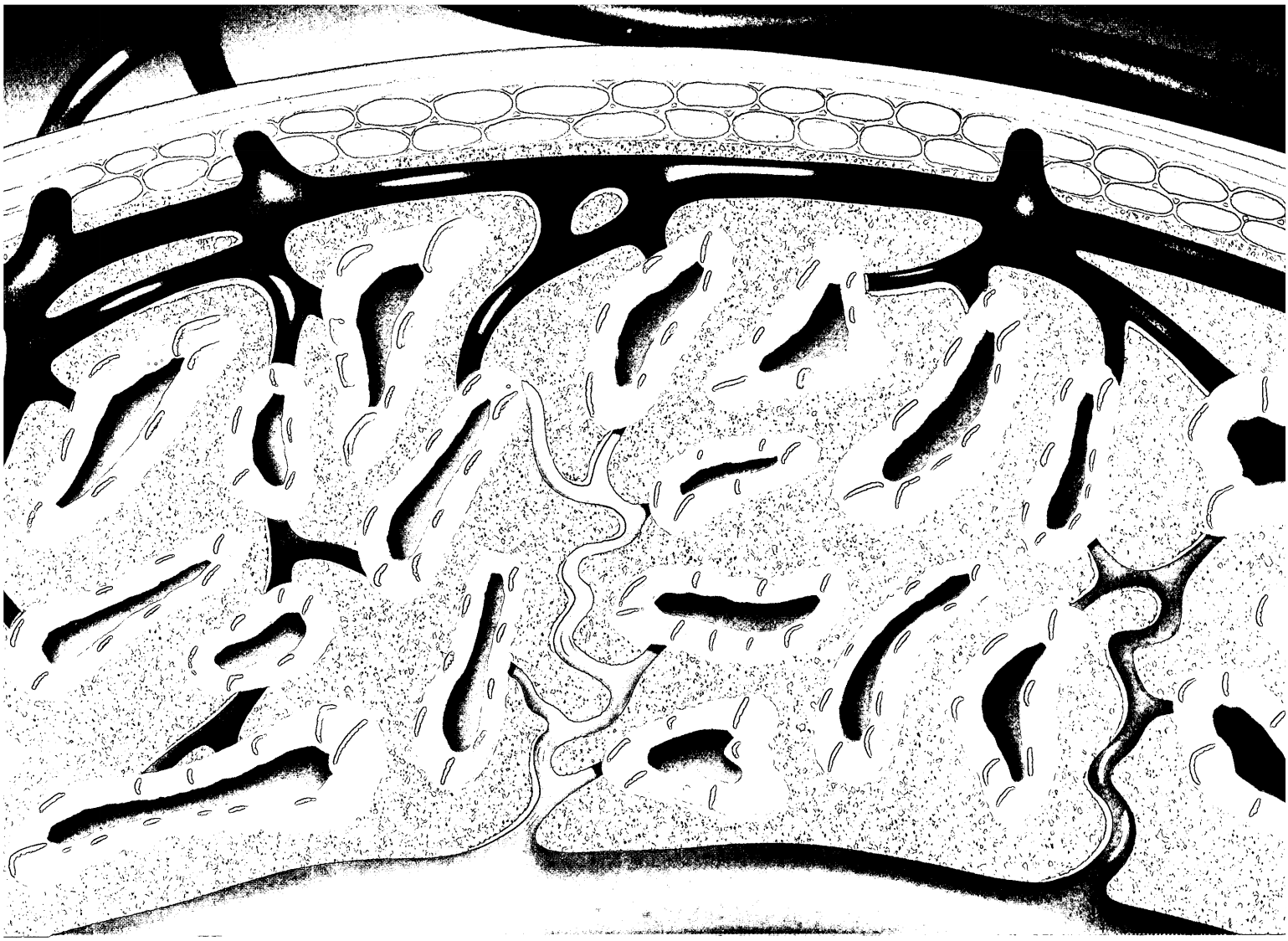
GLUCOMETER ELITE®
Diabetes Care System

The meter designed with your patients in mind.

Making Diabetes Manageable

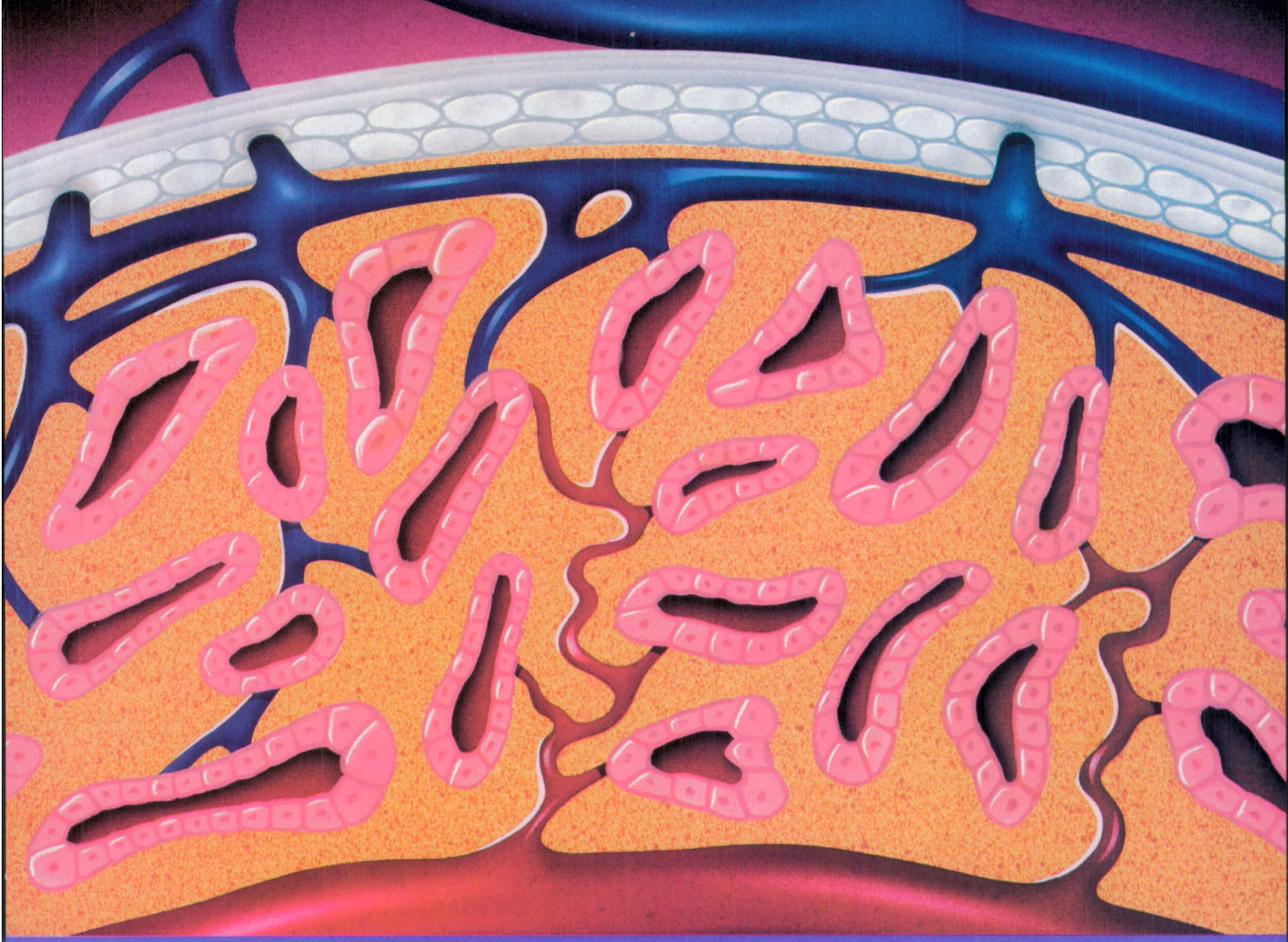
Bayer

Diagnostics Division
Bayer Corporation
Tarrytown, NY 10591



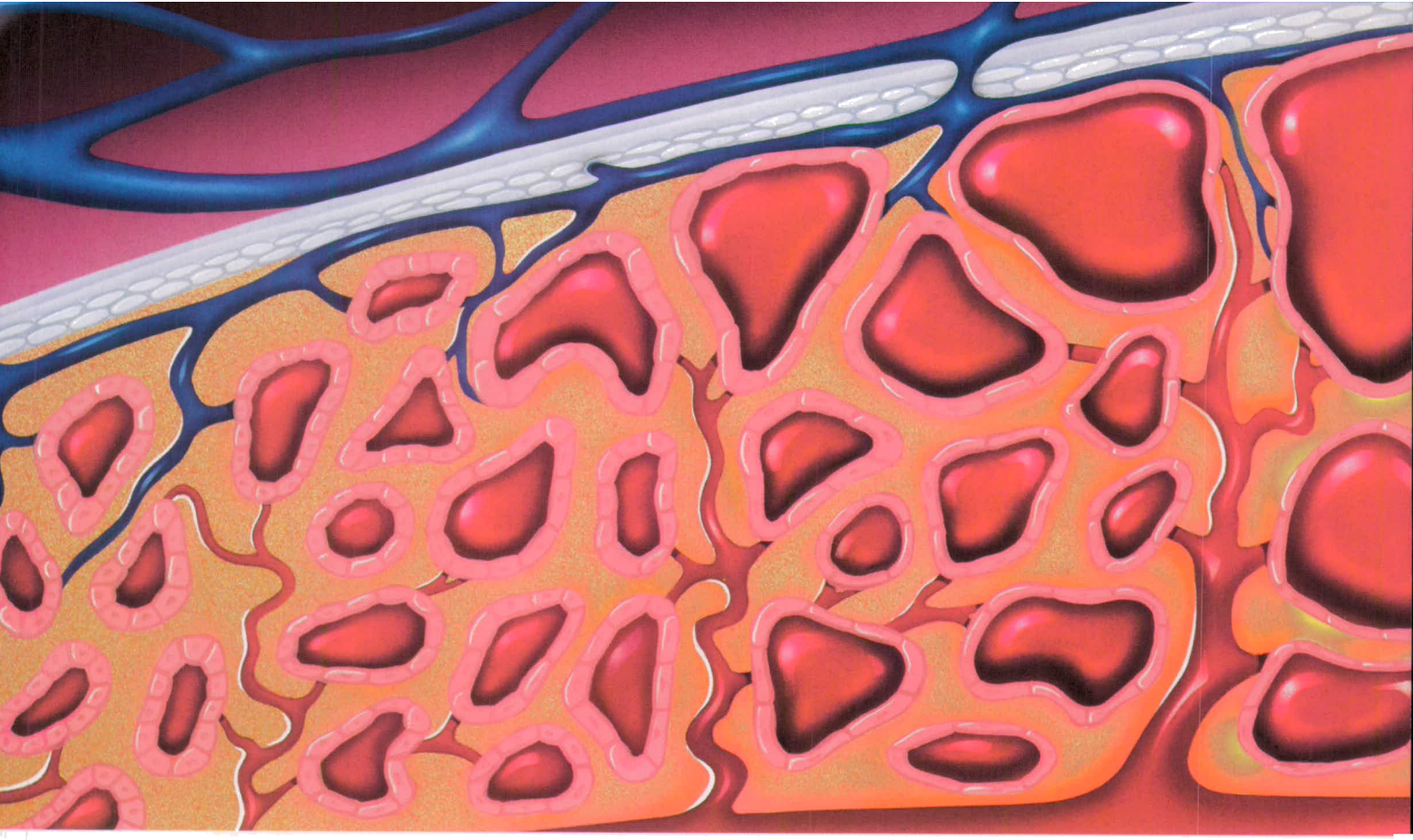
PHYSIOLOGIC OR PSYCHOLOGIC

Erectile Dysfunction Is a Profound Problem Affecting 10 to 20 Million Americans[1]



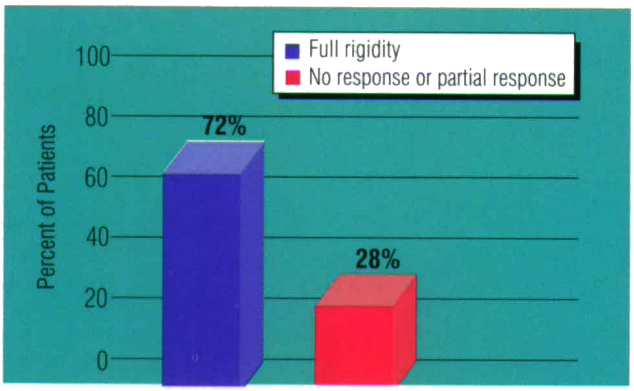
PHYSIOLOGIC OR PSYCHOLOGIC

Erectile Dysfunction Is a Profound Problem Affecting 10 to 20 Million Americans[1]



EFFECTIVE RESULTS

Overall response to CAVERJECT by clinical evaluation[2]



From the open-label, dose-escalation phase of a multicenter, randomized, double-blind, placebo-controlled crossover study. Of 153 patients randomized into the study, 105 patients completed the dose-ranging phase and entered the self-injection phase.

- **72% EFFECTIVE IN OFFICE:** 76 of 105 patients titrated to an optimum dose received at least one evaluation of full rigidity.*[2] Placebo produced no response in the double-blind arm of the study.[2]
- **89% EFFECTIVE AT HOME:** In the 4-week self-injection arm of the study, 91 of 102 patients reported a response to injections at home.†[2] At-home therapy requires proper training of the patient in self-injection.
- **EFFECTIVE THERAPY:** Intracavernosal injection therapy with CAVERJECT is indicated in patients with erectile dysfunction due to vasculogenic, neurogenic, psychogenic, or mixed etiology.‡[2,3]

*Assessments of erection response were recorded at 5, 10, 15, 30, and 120 minutes after injection.

†Patients previously received self-injection training and titration to an optimum dose (a dose that induced an erection sufficient for intercourse). Response was defined as a full or partial erection leading to satisfactory intercourse.

‡Underlying treatable medical causes of erectile dysfunction should be diagnosed and treated prior to initiating therapy with CAVERJECT. CAVERJECT is contraindicated in men with known hypersensitivity to the drug or conditions that might predispose them to priapism, and in men with penile implants or anatomical deformities of the penis.

§Patients should contact their physician or seek immediate medical assistance if an erection persists longer than 6 hours.

‖In one self-injection clinical study where duration of use was up to 18 months, the incidence of fibrosis was 7.8%.

Please see adjacent page for brief summary of prescribing information.

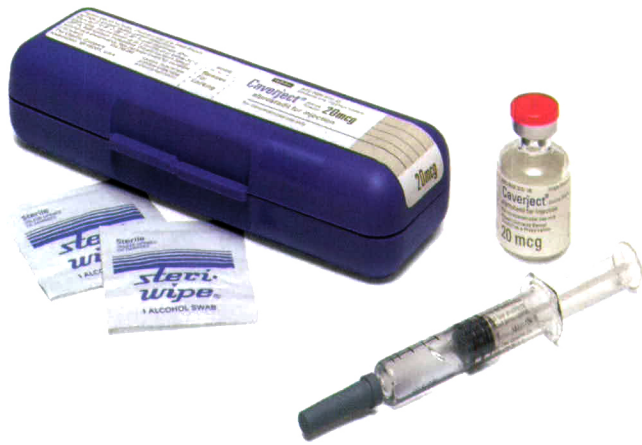
New

Caverject® Sterile Powder
alprostadil for injection

Proven Effective Treatment

CAVERJECT contains alprostadil, the naturally occurring form of prostaglandin E_1 (PGE_1) and is available in a single-dose system with a self-locking case for safe disposal. Each system includes a disposable syringe prefilled with diluent, a vial of 10 or 20 mcg of CAVERJECT Sterile Powder, two alcohol swabs, plus a patient instruction leaflet.

The reconstituted vial of CAVERJECT is for single use only. Patients must properly discard needles after one use and never share them. **Because injections may cause a small amount of bleeding at the injection site, patients should be counseled about the protective measures necessary to guard against sexually transmitted diseases.**



CAVERJECT® Sterile Powder (brand of alprostadil for injection) **For Intracavernosal Use**

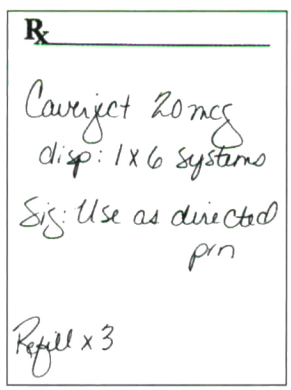
INDICATIONS AND USAGE
Treatment of erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed etiology; also an adjunct to other diagnostic tests in the diagnosis of erectile dysfunction.

CONTRAINDICATIONS
Known hypersensitivity to the drug; conditions that might predispose the patient to priapism, such as sickle cell anemia or trait, multiple myeloma, or leukemia; anatomical penile deformity, such as angulation, cavernosal fibrosis, or Peyronie's disease; and penile implants. Do not use CAVERJECT in women, children, or newborns or in men who should not engage in sexual activity.

PRECAUTIONS
General Precautions: Priapism (erection lasting over 6 hours) can occur. Instruct the patient to immediately report and seek medical assistance for any erection that lasts longer than 6 hours. Treat priapism according to established medical practice. Penile fibrosis, including Peyronie's disease, occurred in 3% of patients in clinical studies (incidence was 7.8% in one 18-month study). Use regular patient follow-up, with careful examination of the penis, to detect signs of penile fibrosis. Stop treatment with CAVERJECT in patients who develop penile angulation, cavernosal fibrosis, or Peyronie's disease. Anticoagulant therapy (such as warfarin or heparin) may increase the tendency for bleeding after injection.

Diagnose and treat underlying treatable medical causes of erectile dysfunction before starting therapy with CAVERJECT. CAVERJECT combined with other vasoactive agents was not systematically studied; the use of such combinations is not recommended. Instruct the patient not to reuse or share needles or syringes and not to let anyone else use his prescription medicines.

Patient Information: Thorough training in self-injection technique is required before CAVERJECT can be used at home. The dose is established in the physician's office. Carefully follow preparation instructions included with each package of CAVERJECT. Discard vials with precipitates or discoloration. The vial is designed for single use; therefore, discard the vial and any remaining solution once the proper amount is withdrawn. Properly discard needle after use; do not reuse or share with others. Do not change the prescribed dose without physician consultation. CAVERJECT should produce an erection in 5 to 20 minutes. Generally, do not exceed an injection frequency of three times per week; separate each use by at least 24 hours. Patients should know the possible side effects of CAVERJECT and what to do if side effects occur. Patients must return for regular check-ups for treatment benefit and safety assessments. Counsel patients about protective measures necessary to guard against the spread of sexually transmitted diseases, including the human immunodeficiency virus (HIV). The small amount of injection-site bleeding that can occur in some patients (see ADVERSE REACTIONS) could increase the risk of transmitting blood-borne diseases between partners.


Rx

Caverject 20 mcg
disp: 1 x 6 systems
Sig: Use as directed prn

Refill x 3

Drug Interactions: In clinical trials, concomitant use of antihypertensive drugs, diuretics, antidiabetic agents (including insulin), or nonsteroidal anti-inflammatory drugs had no effect on the efficacy and safety of CAVERJECT. Pharmacokinetic drug-drug interactions between alprostadil and other agents were not formally studied.

Carcinogenesis, Mutagenesis, and Fertility Impairment: Long-term carcinogenicity studies were not conducted. Alprostadil did not adversely affect or alter spermatogenesis in rats. Mutagenicity tests revealed no potential for mutagenesis. In a 1-year irritancy study in monkeys, there was no evidence of drug-related penile irritancy or nonpenile tissue lesions that could be directly related to alprostadil; any lesions noted were reversible; and histologic changes in the penis had regressed at the end of the 4-week recovery period.

PREGNANCY, NURSING MOTHERS, AND PEDIATRIC USE
CAVERJECT is not for use in newborns, children, or women.

ADVERSE REACTIONS
Local Reactions: Reported by 1% or more of patients treated with CAVERJECT (n=1,861): penile pain (33%, compared with 2% of 294 patients injected with placebo); prolonged erection (4%); penile fibrosis (3%, see PRECAUTIONS); injection-site hematoma (3%); penis disorder (3%, includes numbness, yeast infection, irritation, sensitivity, phimosis, pruritus, erythema, venous leak, penile skin tear, strange feeling of penis, penile head discoloration, and itch at tip of penis); injection-site ecchymosis (2%); penile rash (1%); and penile edema (1%). Penile pain was mild or moderate in intensity in most cases; 3% of patients stopped treatment because of penile pain. In most cases, spontaneous detumescence followed prolonged erection (erection that lasts 4 to 6 hours) and priapism (erection that lasts longer than 6 hours; 0.4% in clinical trials). Titrate CAVERJECT slowly to the lowest effective dose to minimize the chance of prolonged erection or priapism (see DOSAGE AND ADMINISTRATION). Instruct the patient to immediately report and seek medical assistance for any erection that persists longer than 6 hours. Failure to treat priapism immediately may result in penile tissue damage and permanent loss of potency. Most cases of hematoma and ecchymosis were attributed to faulty injection technique. Local reactions reported by less than 1% of patients: balanitis, injection-site hemorrhage, injection-site inflammation, injection-site itching, injection-site swelling, injection-site edema; urethral bleeding; penile warmth; numbness; yeast infection; irritation; sensitivity; phimosis; pruritus; erythema; venous leak; painful erection; and abnormal ejaculation.
Systemic Events: Reported by 1% or more of patients treated with CAVERJECT (n=1,861): upper respiratory tract infection (4%); hypertension (2%); headache (2%); flu syndrome (2%); sinusitis (2%); prostatic disorder (2%, includes prostatitis, pain, hypertrophy, and enlargement); localized pain (2%); trauma (2%); dizziness (1%); back pain (1%); nasal congestion (1%); and cough (1%). Systemic events judged by investigators to be possibly related to the use of CAVERJECT were reported for less than 1% of patients and included testicular pain, scrotal disorder, scrotal edema, hematuria, testicular disorder, impaired urination, urinary frequency, urinary urgency, pelvic pain, hypotension, vasodilation, peripheral vascular disorder, supraventricular extrasystole, vasovagal reactions, hypesthesia, nongeneralized weakness, non-application-site pruritus, skin neoplasm, nausea, dry mouth, increased serum creatinine, leg cramps, and mydriasis. Blood pressure decreases and pulse rate increases were observed in clinical studies and appeared to be dose related (seen principally at doses above 20 micrograms and above 30 micrograms of alprostadil, respectively); changes were usually clinically unimportant (3% of patients stopped because of symptomatic hypotension). CAVERJECT had no clinically important effect on serum or urine laboratory tests.

OVERDOSAGE
If intracavernous overdose with CAVERJECT occurs, place patient under medical supervision until any systemic effects have resolved and penile detumescence has occurred. Symptomatic treatment of systemic symptoms is appropriate.

DOSAGE AND ADMINISTRATION
Individualize each patient's dose by careful physician-supervised titration, following the initial titration guidelines in the product package insert. Doses greater than 60 micrograms are not recommended. In general, use the lowest possible effective dose. A 1/2-inch, 27- to 30-gauge needle is generally recommended.
Initial Titration in Physician's Office: Follow the initial titration instructions that appear in the product package insert; dosage titration instructions differ depending on erectile dysfunction etiology. In one clinical study, 56% of patients were titrated to doses of greater than 5 micrograms but less than or equal to 20 micrograms; the mean dose at the end of titration was 17.8 micrograms.
Maintenance Therapy: Properly instruct and train the patient in the self-injection technique, and carefully assess the patient's skills and competence with this procedure before starting self-injection therapy. The dose selected for self-injection therapy should provide an erection that is satisfactory for sexual activity and is maintained for no longer than 1 hour. Reduce the dose if the erection lasts longer than 1 hour. Dose adjustments for self-injection, if required, should only be made with physician consultation and should follow initial titration guidelines. CAVERJECT was effective for up to 6 months in an uncontrolled, self-injection study; the mean dose at the end of 6 months was 20.7 micrograms. Exercise careful and continuous follow-up of patients on self-injection therapy, especially for initial self-injections. Recommended injection frequency is no more than three times weekly, with at least 24 hours between uses. Instruct the patient in the proper disposal of the syringe, needle, and single-use vial. See the patient every 3 months during self-injection therapy to assess treatment and, if needed, to adjust the dose.

CAVERJECT as an Adjunct to the Diagnosis of Erectile Dysfunction: In pharmacologic diagnostic testing for erectile dysfunction, monitor patients for the occurrence of an erection after an intracavernosal injection of CAVERJECT. Use CAVERJECT as an adjunct to laboratory investigations to allow visualization and assessment of penile vasculature. For these tests, use a single dose of CAVERJECT that induces a firm and rigid erection.

Solution Preparation: Refer to product package insert for reconstitution instructions. One mL of sterile water preserved with 0.945% w/v benzyl alcohol or bacteriostatic water for injection with benzyl alcohol must be used for reconstitution. Use the solution immediately after reconstitution; do not store or freeze. Inspect reconstituted solution visually for particulate matter.

HOW SUPPLIED
CAVERJECT is a dry, lyophilized powder in vials containing 11.9 micrograms or 23.2 micrograms of alprostadil for intracavernosal administration (10 or 20 micrograms, respectively, of deliverable alprostadil when reconstituted as directed). Use only the accompanying diluent or bacteriostatic water for injection with benzyl alcohol to reconstitute CAVERJECT. Use reconstituted solution immediately; do not store or freeze.

6—10-microgram vials with diluent syringe - NDC 0009-3778-08
6—20-microgram vials with diluent syringe - NDC 0009-3701-01

CAUTION: Federal law prohibits dispensing without a prescription.

Store vials at refrigerated temperatures of 2°C to 8°C (36°F to 46°F) until dispensed. After dispensing, unused packages of CAVERJECT Sterile Powder may be stored up to 3 months at or below 25°C (77°F).

B-1-S

References
1. The NIH Consensus Development Panel on Impotence. The NIH Consensus Conference: impotence. *JAMA.* 1993;270:83-90.
2. Data on file, TR9124-93-006. The Upjohn Company, Kalamazoo, Mich.
3. Data on file, TR9124-93-005. The Upjohn Company, Kalamazoo, Mich.
4. Data on file, NDA Application Summary, Item 2, Vol 1.2. The Upjohn Company, Kalamazoo, Mich.

Upjohn

USJ 2685.00 September 1995