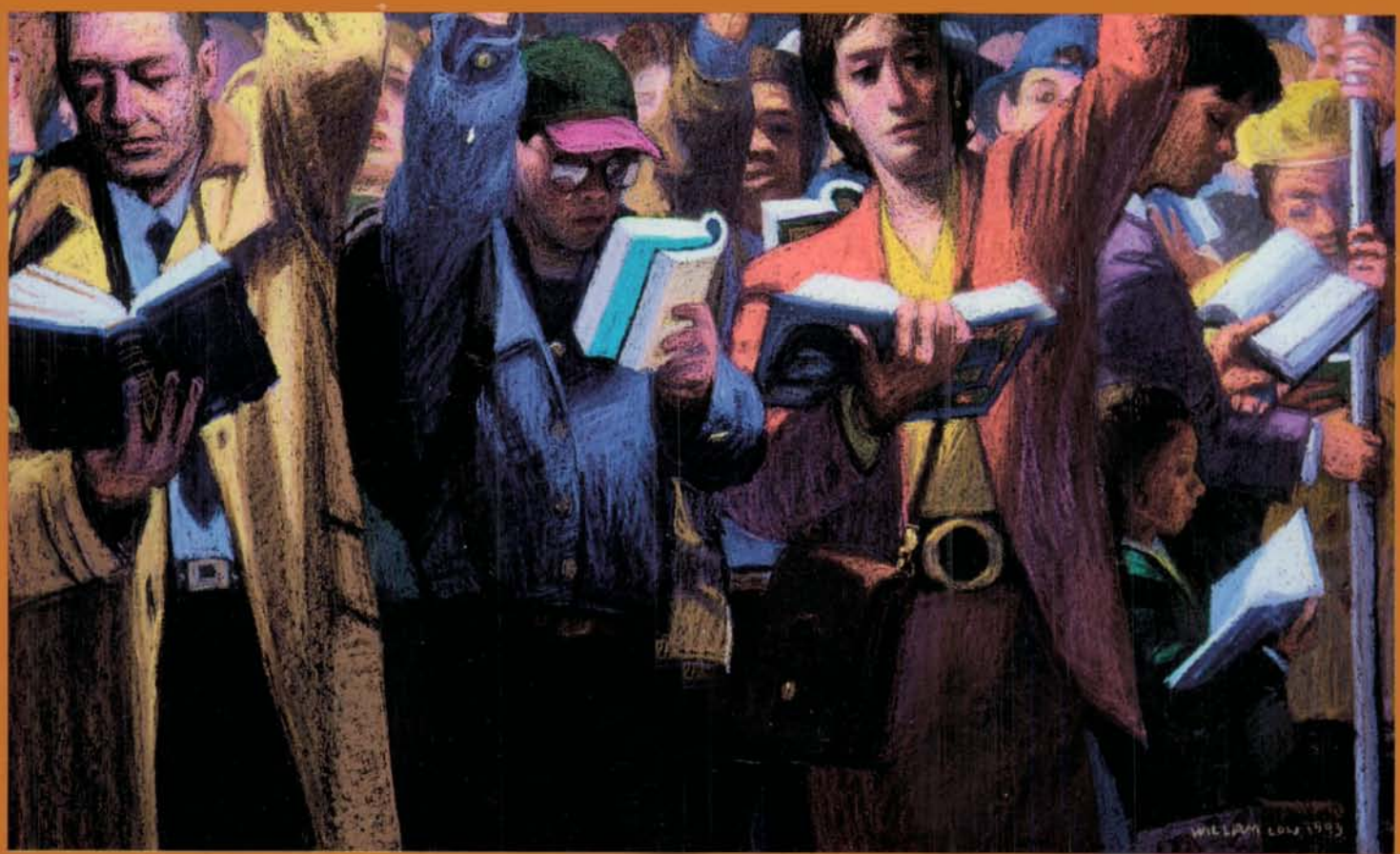
THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

VOLUME 20 NUMBER 6

Diabetes Care

JUNE 1997 WWW.DIABETES.ORG/DIABETESCARE



American Diabetes Association.

ISSN 0149-5992


Now that they have diabetes...
40
* Non–insulin-dependent diabetes mellitus.
† Gastrointestinal therapeutic system.
As with all sulfonylureas, hypoglycemia may occur.
Please see brief summary of prescribing information on the adjacent page.

they know how crucial diet and exercise are.

Since it's hard to change lifestyle, their first diabetic agent should be easy.

Choose it for **control.**

Choose it for **convenience.**

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When diet alone fails in NIDDM*...

ONCE DAILY **GlucotrolXL®**

(glipizide) extended release

Tablets 5 mg and 10 mg GITS

GLUCOTROL XL® (glipizide) Extended Release Tablets *For Oral Use*

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 - arthralgia, 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.

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THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

VOLUME 20 NUMBER 6

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 to the editor, Charles M. Clark, Jr., MD, *Diabetes Care* Editorial Office, Regenstrief Institute, 6th Floor, 1001 West Tenth Street, Indianapolis, IN 46202-2859; (317) 630-6925.

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* 336:309–315, 1997. "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 $110 in the U.S., Canada, and Mexico (for Canada add 7% GST) and $170 for all other countries. Institutional rates are $180 in the U.S., Canada, and Mexico (for Canada add 7% GST) and $240 in all other countries. Professional membership includes $75 designated for *Diabetes Care*. Single issues are $13.50 in the U.S., Canada, and Mexico (Canada add 7% GST) and $17.00 in all other countries. Periodical 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, 1660 Duke St., Alexandria, VA 22314.

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

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Diabetes Care

▶ = Cover articles. Also available on the World Wide Web at www.diabetes.org/diabetescare

Editorial

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Emerging Treatments and Technologies

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Reviews/Commentaries/Position Statements

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Letters

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(VOLUME 20, NUMBER 6)

COVER: *Straphangers* by William Low, March 1992. Pastel on paper, 16" × 27".

Practical Approaches in Diabetes Care

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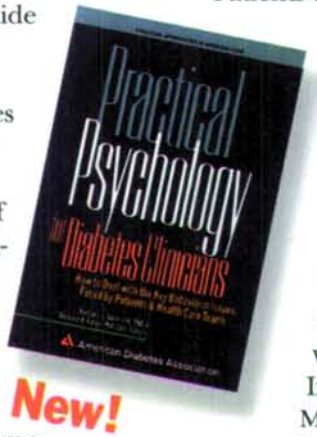

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Using the Empowerment Approach • The Therapeutic Alliance: Provider Burnout • Understanding and Treating "Diabetes Burnout" • Psychological Issues Facing Newly Diagnosed Patients

Diabetes Education Goals

Features the most up-to-date advice on how to assess, plan, and evaluate patient education and counseling programs, including the recently revised content areas recommended by the National Diabetes Advisory Board.

Divided into sections on IDDM, NIDDM, and GDM, the book covers short-term, survival goals, and continuing, in-depth goals. Features sections devoted to age-sensitive considerations as well as approaches for educating patients with special challenges to learning. Much more than a series of checklists, the book focuses on the education process and emphasizes assessing the unique needs of each patient. Softcover, 64 pages. #PEDEG
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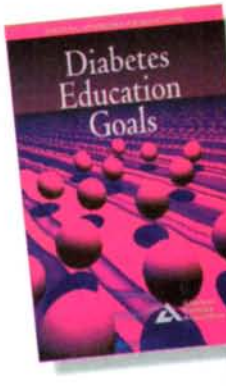

Contents:

Elements of Successful Education • Elements of Teaching and Learning • Type I Diabetes: *Initial Education Goals; Continuing Education Goals* • Type II Diabetes: *Initial Education Goals; Continuing Education Goals; Special Considerations* • Diabetes and Pregnancy: *Pregnancy with Preexisting Diabetes; Gestational Diabetes* • Diabetes Through Life Stages • Educational Approaches for Special Situations

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Also, Cardura is well tolerated. The side effects reported significantly more often than placebo in hypertension studies were dizziness, somnolence, and fatigue. These were generally mild and transient. Only 2% of patients discontinued therapy due to adverse effects—the same as with placebo. Syncope has been reported, but rarely (<1%). Therefore, as with all alpha blockers, careful titration and blood pressure monitoring is important.

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Please see brief summary of prescribing information on adjacent page.

TAKES THE PRESSURE OFF

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References: 1. Neaton JD, Grimm RH Jr, Prineas RJ, et al, for the Treatment of Mild Hypertension Study Research Group. Treatment of Mild Hypertension Study: final results. *JAMA.* 1993;270:713-724. **2.** Soltero I, Guevara J, Silva H, Velasco M. A multicenter study of doxazosin in the treatment of severe essential hypertension. *Am Heart J.* 1988;116:1767-1771. **3.** Ferrara LA, Di Marino L, Russo O, Marotta T, Mancini M, on behalf of the DoCHH Study Group. Doxazosin and captopril in mildly hypercholesterolemic hypertensive patients: the Doxazosin-Captopril in Hypercholesterolemic Hypertensives Study. *Hypertension.* 1993;21:97-104. **4.** Lehtonen A, the Finnish Multicenter Study Group. Lowered levels of serum insulin, glucose, and cholesterol in hypertensive patients during treatment with doxazosin. *Current Therapeutic Research.* 1990;47:278-284.

CARDURA® (doxazosin mesylate) Tablets
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

CARDURA (doxazosin mesylate) is indicated for the treatment of hypertension. CARDURA may be used alone or in combination with diuretics or beta-adrenergic blocking agents. There is limited experience with CARDURA in combination with angiotensin converting enzyme inhibitors or calcium channel blockers.

CONTRAINDICATIONS

CARDURA is contraindicated in patients with a known sensitivity to quinazolines (e.g. prazosin, terazosin).

WARNINGS

Syncope and "First-dose" Effect:

Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION section) with increases in dose every two weeks. Additional antihypertensive agents should be added with caution.

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 hours after the first dose necessitating termination of the study. In this study 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials involving over 1500 patients with dose titration every one to two weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

PRECAUTIONS

General

1. Orthostatic Hypotension:

While syncope is the most severe orthostatic effect of CARDURA, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo, can occur, especially at initiation of therapy or at the time of dose increases. These were common in clinical trials, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo controlled titration trials orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution.

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA.

2. Impaired liver function:

CARDURA should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism. There is no controlled clinical experience with CARDURA in patients with these conditions.

3. Leukopenia/Neutropenia:

Analysis of hematologic data from patients receiving CARDURA in controlled clinical trials showed that the mean WBC (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. A search through a data base of 2400 patients revealed 4 in which drug-related neutropenia could not be ruled out. Two had a single low value on the last day of treatment. Two had stable, non-progressive neutrophil counts in the 1000/mm³ range over periods of 20 and 40 weeks. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA. No patients became symptomatic as a result of the low WBC or neutrophil counts.

Information for Patients:

Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with doxazosin, requiring caution in people who must drive or operate heavy machinery.

Drug Interactions:

Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that CARDURA has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta blocking agents, and nonsteroidal anti-inflammatory drugs.

Cimetidine:

In a placebo-controlled trial in normal volunteers, the administration of a single 1 mg dose of doxazosin on day 1 of a four-day regimen of oral cimetidine (400 mg twice daily) resulted in a 10% increase in mean AUC of doxazosin (p=0.006), and a slight but not statistically significant increase in mean C_{max} and mean half-life of doxazosin. The clinical significance of this increase in doxazosin AUC is unknown.

Drug/Laboratory test interactions:

None known.

Cardiac Toxicity in Animals:

An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (150 times the maximum recommended human dose assuming a patient weight of 60 kg). Myocardial fibrosis was observed in both rats and mice treated in the same manner with 40 mg doxazosin/kg/day for 18 months. No cardiotoxicity was observed at lower doses (up to 10 or 20 mg/kg/day, depending on the study) in either species. These lesions were not observed after 12 months of oral dosing in dogs and Wistar rats at maximum doses of 20 mg/kg/day and 100 mg/kg/day, respectively. There is no evidence that similar lesions occur in humans.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated concentrations (highest dose 40 mg/kg: about 150 times the maximum recommended human dose of 16 mg/60 kg) revealed no evidence of carcinogenicity in rats. There was also no evidence of carcinogenicity in a similarly conducted study (up to 18 months of dietary administration) in mice. The mouse study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 75 times the maximum recommended human dose. This effect was reversible within two weeks of drug withdrawal.

Pregnancy

Teratogenic Effects, Pregnancy Category C. Studies in pregnant rabbits and rats at daily oral doses of up to 41 and 20 mg/kg, respectively (154 and 75 times the maximum recommended daily dose of 16 mg, assuming a patient weight of 60 kg), have revealed no evidence of harm to the fetus. A dosage regimen of 82 mg/kg/day in the rabbit was associated with reduced fetal survival. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

Nonteratogenic Effects. In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin was delayed as evidenced by slower body weight gain and a slightly later appearance of anatomical features and reflexes.

Nursing Mothers

Studies in lactating rats given a single oral dose of 1 mg/kg of [2-^{14}C]-doxazosin indicate that doxazosin accumulates in rat breast milk with a maximum concentration about 20 times greater than the maternal plasma concentration. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARDURA is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

CARDURA has been administered to approximately 4000 patients, of whom 1679 were included in the clinical development program. In that program, minor adverse effects were frequent, but led to discontinuation of treatment in only 7% of patients. In placebo-controlled studies adverse effects occurred in 49% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group. The major reasons for discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0.7%.

In controlled clinical trials directly comparing CARDURA to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue/malaise. Postural effects and edema appeared to be dose related.

The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. The following summarizes those adverse experiences (possibly/probably related) reported for patients in these studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

Adverse reactions during placebo-controlled studies with doxazosin (n=339) and placebo (n=336), respectively: Cardiovascular—*Dizziness:* 19% and 9%; *Vertigo:* 2% and 1%; *Postural Hypotension:* 0.3% and 0%; *Edema:* 4% and 3%; *Palpitation:* 2% and 3%; *Arrhythmia:* 1% and 0%; *Hypotension:* 1% and 0%; *Tachycardia:* 0.3% and 1%; *Peripheral Ischemia:* 0.3% and 0%; **Skin Appendages**—*Rash:* 1% and 1%; *Pruritus:* 1% and 1%; **Musculoskeletal**—*Arthralgia/Arthritis:* 1% and 0%; *Muscle Weakness:* 1% and 0%; *Myalgia:* 1% and 0%; **Central & Peripheral N.S.**—*Headache:* 14% and 16%; *Paresthesia:* 1% and 1%; *Kinetic Disorders:* 1% and 0%; *Ataxia:* 1% and 0%; *Hypertonia:* 1% and 0%; *Muscle Cramps:* 1% and 0%; **Autonomic**—*Mouth Dry:* 2% and 2%; *Flushing:* 1% and 0%; **Special Senses**—*Vision Abnormal:* 2% and 1%; *Conjunctivitis/Eye Pain:* 1% and 1%; *Tinnitus:* 1% and 0.3%; **Psychiatric**—*Somnolence:* 5% and 1%; *Nervousness:* 2% and 2%; *Depression:* 1% and 1%; *Insomnia:* 1% and 1%; *Sexual Dysfunction:* 2% and 1%; **Gastrointestinal**—*Nausea:* 3% and 4%; *Diarrhea:* 2% and 3%; *Constipation:* 1% and 1%; *Dyspepsia:* 1% and 1%; *Flatulence:* 1% and 1%; *Abdominal Pain:* 0% and 2%; *Vomiting:* 0% and 1%; **Respiratory**—*Rhinitis:* 3% and 1%; *Dyspnea:* 1% and 1%; *Epistaxis:* 1% and 0%; **Urinary**—*Polyuria:* 2% and 0%; *Urinary Incontinence:* 1% and 0%; *Micturation Frequency:* 0% and 2%; **General**—*Fatigue/Malaise:* 12% and 6%; *Chest Pain:* 2% and 2%; *Asthenia:* 1% and 1%; *Face Edema:* 1% and 0%; *Pain:* 2% and 2%.

Additional adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency of between 0.5% and 1%: syncope, hypoesthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-term clinical studies, including international studies. *Cardiovascular System:* angina pectoris, myocardial infarction, cerebrovascular accident; *Autonomic Nervous System:* pallor; *Metabolic:* thirst, gout, hypokalemia; *Hematopoietic:* lymphadenopathy, purpura; *Reproductive System:* breast pain; *Skin Disorders:* alopecia, dry skin, eczema; *Central Nervous System:* paresis, tremor, twitching, confusion, migraine, impaired concentration; *Psychiatric:* paroniria, amnesia, emotional lability, abnormal thinking, depersonalization; *Special Senses:* parosmia, earache, taste perversion, photophobia, abnormal lacrimation; *Gastrointestinal System:* increased appetite, anorexia, fecal incontinence, gastroenteritis; *Respiratory System:* bronchospasm, sinusitis, coughing, pharyngitis; *Urinary System:* renal calculus; *General Body System:* hot flushes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests. CARDURA has been associated with decreases in white blood cell counts (See Precautions).

OVERDOSAGE

No data are available in regard to overdosage in humans.

The oral LD_{50} of doxazosin is greater than 1000 mg/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid. As doxazosin is highly protein bound, dialysis would not be indicated.

DOSAGE AND ADMINISTRATION

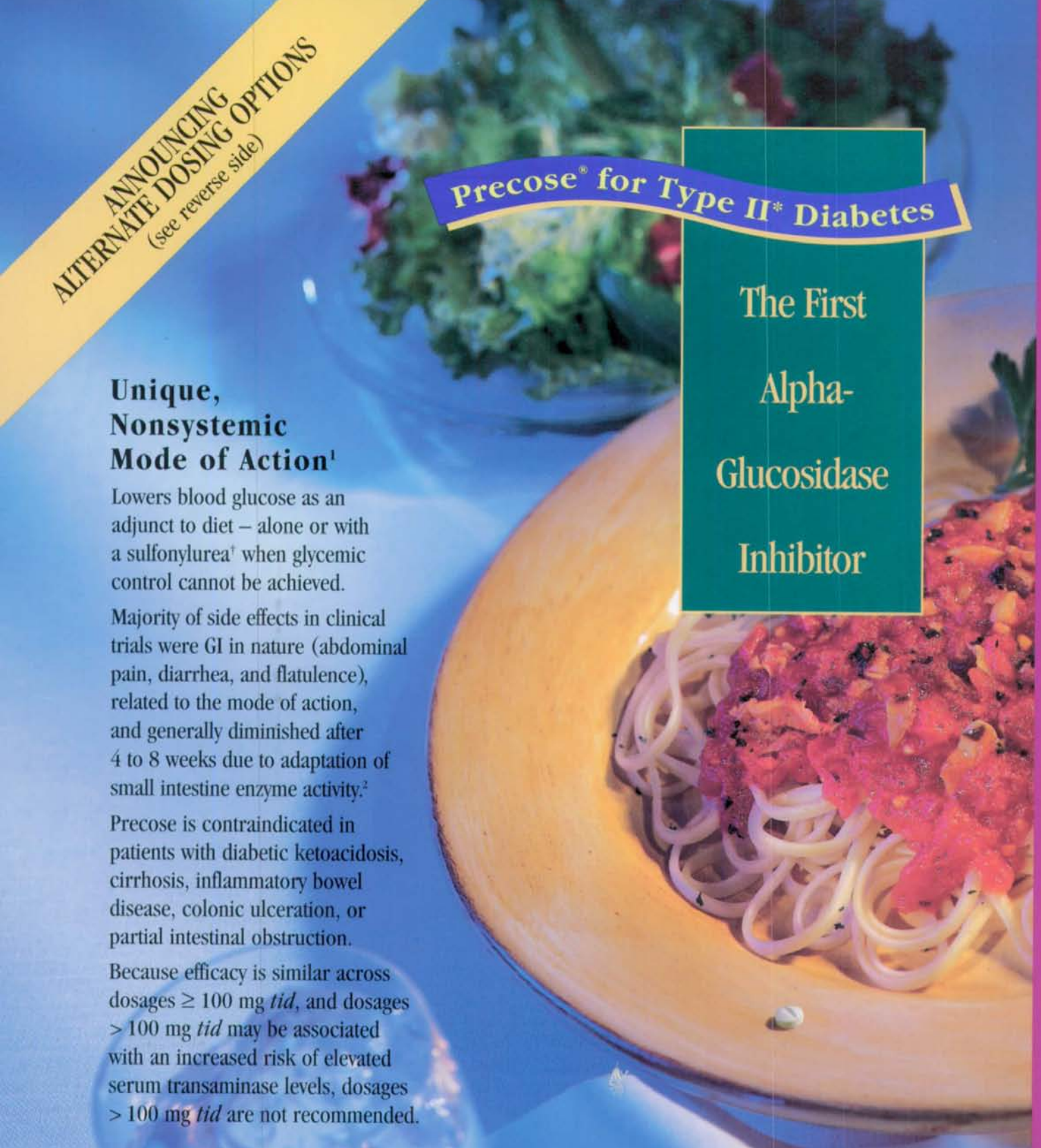
DOSAGE MUST BE INDIVIDUALIZED. The initial dosage of CARDURA in hypertensive patients is 1 mg given once daily. This starting dose is intended to minimize the frequency of postural hypotension and first dose syncope associated with CARDURA. Postural effects are most likely to occur between 2 and 6 hours after a dose. Therefore blood pressure measurements should be taken during this time period after the first dose and with each increase in dose. Depending on the individual patient's standing blood pressure response (based on measurements taken at 2-6 hours postdose and 24 hours postdose), dosage may then be increased to 2 mg and thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve the desired reduction in blood pressure. **Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo, postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.**

More detailed professional information available on request.

65-4538-00-1 Revised January 1993

Pfizer U.S. Pharmaceuticals Group

ANNOUNCING
ALTERNATE DOSING OPTIONS
(see reverse side)



Precose® for Type II* Diabetes

The First Alpha-Glucosidase Inhibitor

Unique, Nonsystemic Mode of Action[1]

Lowers blood glucose as an adjunct to diet – alone or with a sulfonylurea† when glycemic control cannot be achieved.

Majority of side effects in clinical trials were GI in nature (abdominal pain, diarrhea, and flatulence), related to the mode of action, and generally diminished after 4 to 8 weeks due to adaptation of small intestine enzyme activity.[2]

Precose is contraindicated in patients with diabetic ketoacidosis, cirrhosis, inflammatory bowel disease, colonic ulceration, or partial intestinal obstruction.

Because efficacy is similar across dosages ≥ 100 mg *tid*, and dosages > 100 mg *tid* may be associated with an increased risk of elevated serum transaminase levels, dosages > 100 mg *tid* are not recommended.

* Non-insulin-dependent diabetes mellitus.

† Precose itself does not cause hypoglycemia. When used in combination with sulfonylureas, it may increase their hypoglycemic potential. Oral glucose, whose absorption is not inhibited by Precose, should be used instead of sucrose in the treatment of mild to moderate hypoglycemia.

Please see brief summary of Prescribing Information on adjacent page.

50 mg, 100 mg

Precose®

(acarbose tablets)

NIDDM management from the first bite.

50 mg, 100 mg

Precose®

(acarbose tablets)

Dosage and Administration

Taken With the First Bite of Each Main Meal	
Initial dosage:	25 mg *tid* (half of a scored 50-mg tablet *tid*)
Alternate Initial Dosage to Minimize GI Side Effects	
Initial dosage:	25 mg *once daily* (taken with the first bite of the main meal)
Gradually titrate to:	25 mg *tid*
Titrate to:	50 mg *tid*
Maintenance dosage:	50 mg *tid* to 100 mg *tid*
Maximum dosages:	50 mg *tid* for patients ≤ 132 lb 100 mg *tid* for patients > 132 lb

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

PZ500036BS 4/96

INDICATIONS AND USAGE

PRECOSE®, as monotherapy, is indicated as an adjunct to diet to lower blood glucose in patients with non-insulin-dependent diabetes mellitus (NIDDM) whose hyperglycemia cannot be managed on diet alone. PRECOSE® may also be used in combination with a sulfonylurea when diet plus either PRECOSE® or a sulfonylurea do not result in adequate glycemic control. The effect of PRECOSE® to enhance glycemic control is additive to that of sulfonylureas when used in combination, presumably because its mechanism of action is different.

In initiating treatment for NIDDM, 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 blood glucose and symptoms of hyperglycemia. The importance of regular physical activity when appropriate should also be stressed. If this treatment program fails to result in adequate glycemic control, the use of PRECOSE® should be considered. The use of PRECOSE® 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.

CONTRAINDICATIONS

PRECOSE® is contraindicated in patients with known hypersensitivity to the drug and in patients with diabetic ketoacidosis or cirrhosis. PRECOSE® is also contraindicated in patients with inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or in patients predisposed to intestinal obstruction. In addition, PRECOSE® is contraindicated in patients who have chronic intestinal diseases associated with marked disorders of digestion or absorption and in patients who have conditions that may deteriorate as a result of increased gas formation in the intestine.

PRECAUTIONS

General

Hypoglycemia: Because of its mechanism of action, PRECOSE® when administered alone should not cause hypoglycemia in the fasted or postprandial state. Sulfonylurea agents may cause hypoglycemia. Because PRECOSE® given in combination with a sulfonylurea will cause a further lowering of blood glucose, it may increase the hypoglycemic potential of the sulfonylurea. Oral glucose (dextrose), whose absorption is not inhibited by PRECOSE®, should be used instead of sucrose (cane sugar) in the treatment of mild to moderate hypoglycemia. Sucrose, whose hydrolysis to glucose and fructose is inhibited by PRECOSE®, is unsuitable for the rapid correction of hypoglycemia. Severe hypoglycemia may require the use of either intravenous glucose infusion or glucagon injection.

Elevated Serum Transaminase Levels: In clinical trials, at doses of 50 mg t.i.d. and 100 mg t.i.d., the incidence of serum transaminase elevations with PRECOSE® was the same as with placebo. In long-term studies (up to 12 months, and including PRECOSE® doses up to 300 mg t.i.d.) conducted in the United States, treatment-emergent elevations of serum transaminases (AST and/or ALT) occurred in 15% of PRECOSE®-treated patients as compared to 7% of placebo-treated patients. These serum transaminase elevations appear to be dose related. At doses greater than 100 mg t.i.d., the incidence of serum transaminase elevations greater than three times the upper limit of normal was two to three times higher in the PRECOSE® group than in the placebo group. These elevations were asymptomatic, reversible, more common in females, and, in general, were not associated with other evidence of liver dysfunction.

In international post-marketing experience with PRECOSE® in over 500,000 patients, 19 cases of serum transaminase elevations > 500 IU/L (12 of which were associated with jaundice) have been reported. Fifteen of these 19 cases received treatment with 100 mg t.i.d. or greater and 13 of 16 patients for whom weight was reported weighed < 60 kg. In the 18 cases where follow-up was recorded, hepatic abnormalities improved or resolved upon discontinuation of PRECOSE®.

Loss of Control of Blood Glucose: When diabetic patients are exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of control of blood glucose may occur. At such times, temporary insulin therapy may be necessary.

Information for Patients: Patients should be told to take PRECOSE® orally three times a day at the start (with the first bite) of each main meal. It is important that patients continue to adhere to dietary instructions, a regular exercise program, and regular testing of urine and/or blood glucose.

PRECOSE® itself does not cause hypoglycemia even when administered to patients in the fasted state. Sulfonylurea drugs and insulin, however, can lower blood sugar levels enough to cause symptoms or sometimes life-threatening hypoglycemia. Because PRECOSE® given in combination with a sulfonylurea or insulin will cause a further lowering of blood sugar, it may increase the hypoglycemic potential of these agents. The risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be well understood by patients and responsible family members. Because PRECOSE® prevents the breakdown of table sugar, patients should have a readily available source of glucose (dextrose, D-glucose) to treat symptoms of low blood sugar when taking PRECOSE® in combination with a sulfonylurea or insulin.

If side effects occur with PRECOSE®, they usually develop during the first few weeks of therapy. They are most commonly mild-to-moderate gastrointestinal effects, such as flatulence, diarrhea, or abdominal discomfort and generally diminish in frequency and intensity with time.

Laboratory Tests: Therapeutic response to PRECOSE® should be monitored by periodic blood glucose tests. Measurement of glycosylated hemoglobin levels is recommended for the monitoring of long-term glycemic control.

PRECOSE®, particularly at doses in excess of 50 mg t.i.d., may give rise to elevations of serum transaminases and, in rare instances, hyperbilirubinemia. It is recommended that serum transaminase levels be checked every 3 months during the first year of treatment with PRECOSE® and periodically thereafter. If elevated transaminases are observed, a reduction in dosage or withdrawal of therapy may be indicated, particularly if the elevations persist.

Renal Impairment: Plasma concentrations of PRECOSE® in renally impaired volunteers were proportionally increased relative to the degree of renal dysfunction. Long-term clinical trials in diabetic patients with significant renal dysfunction (serum creatinine >2.0 mg/dL) have not been conducted. Therefore, treatment of these patients with PRECOSE® is not recommended.

Drug Interactions: Certain drugs tend to produce hyperglycemia and may lead to loss of blood glucose 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 PRECOSE®, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from patients receiving PRECOSE® in combination with sulfonylureas or insulin, patients should be observed closely for any evidence of hypoglycemia.

Intestinal adsorbents (e.g., charcoal) and digestive enzyme preparations containing carbohydrate-splitting enzymes (e.g., amylase, pancreatin) may reduce the effect of PRECOSE® and should not be taken concomitantly.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Nine chronic toxicity/carcinogenicity studies were conducted in three animal species (rat, hamster, dog) including two rat strains (Sprague-Dawley and Wistar).

In the first rat study, Sprague-Dawley rats received acarbose in feed at high doses (up to approximately 500 mg/kg body weight) for 104 weeks. Acarbose treatment resulted in a significant increase in the incidence of renal tumors (adenomas and adenocarcinomas) and benign Leydig cell tumors. This study was repeated with a similar outcome. Further studies were performed to separate direct carcinogenic effects of acarbose from indirect effects resulting from the carbohydrate malnutrition induced by the large doses of acarbose employed in the studies. In one study using Sprague-Dawley rats, acarbose was mixed with feed but carbohydrate deprivation was prevented by the addition of glucose to the diet. In a 26-month study of Sprague-Dawley rats, acarbose was administered by daily postprandial gavage so as to avoid the pharmacologic effects of the drug. In both of these studies, the increased incidence of renal tumors found in the original studies did not occur. Acarbose was also given in food and by postprandial gavage in two separate studies in Wistar rats. No increased incidence of renal tumors was found in either of these Wistar rat studies. In two feeding studies of hamsters, with and without glucose supplementation, there was also no evidence of carcinogenicity.

Acarbose showed no mutagenic activity when tested in six *in vitro* and three *in vivo* assays.

Fertility studies conducted in rats after oral administration produced no untoward effect on fertility or on the overall capability to reproduce.

Pregnancy:

Teratogenic Effects: Pregnancy Category B. The safety of PRECOSE® in pregnant women has not been established. Reproduction studies have been performed in rats at doses up to 480 mg/kg (corresponding to 9 times the exposure in humans, based on drug blood levels) and have revealed no evidence of impaired fertility or harm to the fetus due to acarbose. In rabbits, reduced maternal body weight gain, probably the result of the pharmacodynamic activity of high doses of acarbose in the intestines, may have been responsible for a slight increase in the number of embryonic losses. However, rabbits given 160 mg/kg acarbose (corresponding to 10 times the dose in man, based on body surface area) showed no evidence of embryotoxicity and there was no evidence of teratogenicity at a dose 32 times the dose in man (based on body surface area). There are, however, no adequate and well-controlled studies of PRECOSE® in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed. Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers: A small amount of radioactivity has been found in the milk of lactating rats after administration of radiolabeled acarbose. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, PRECOSE® should not be administered to a nursing woman.

Pediatric Use: Safety and effectiveness of PRECOSE® in pediatric patients have not been established.

ADVERSE REACTIONS

Digestive Tract: Gastrointestinal symptoms are the most common reactions to PRECOSE®. In U.S. placebo-controlled trials, the incidences of abdominal pain, diarrhea, and flatulence were 21%, 33%, and 77% respectively in 1075 patients treated with PRECOSE® 50-300 mg t.i.d., whereas the corresponding incidences were 9%, 12%, and 32% in 818 placebo-treated patients. Abdominal pain and diarrhea tended to return to pretreatment levels over time, and the frequency and intensity of flatulence tended to abate with time. The increased gastrointestinal tract symptoms in patients treated with PRECOSE® is a manifestation of the mechanism of action of PRECOSE® and is related to the presence of undigested carbohydrate in the lower GI tract. Rarely, these gastrointestinal events may be severe and might be confused with paralytic ileus.

Elevated Serum Transaminase Levels: See PRECAUTIONS.

Other Abnormal Laboratory Findings: Small reductions in hematocrit occurred more often in PRECOSE®-treated patients than in placebo-treated patients but were not associated with reductions in hemoglobin. Low serum calcium and low plasma vitamin B_6 levels were associated with PRECOSE® therapy but were thought to be either spurious or of no clinical significance.

Caution: Federal law prohibits dispensing without a prescription.

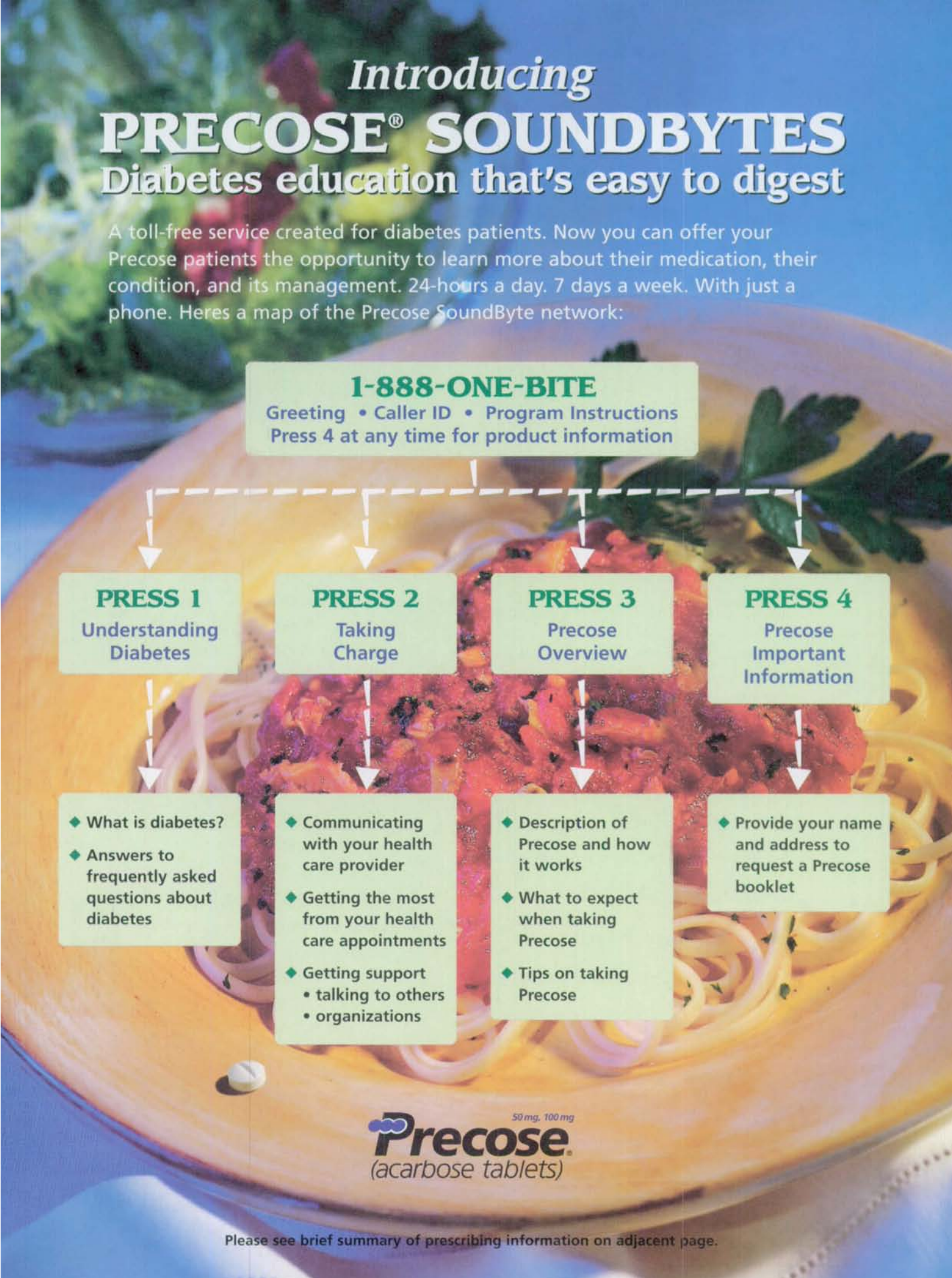
PZ500036BS 4/96 Bay g 5421 PRECOSE®/5202/0/8/USA-1
 6160 Printed in U.S.A.

References

1. Precose® (acarbose tablets) Package Insert.
2. Hanefeld M. Acarbose efficacy review. *Practical Diabetes Suppl.* 1993;10(6):S21-S27.

Bayer

Pharmaceutical Division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PRECOSE® SOUNDBYTES
Diabetes education that's easy to digest
A toll-free service created for diabetes patients. Now you can offer your Precose patients the opportunity to learn more about their medication, their condition, and its management. 24-hours a day. 7 days a week. With just a phone. Heres a map of the Precose SoundByte network:
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Understanding Diabetes
PRESS 2
Taking Charge
PRESS 3
Precose Overview
PRESS 4
Precose Important Information
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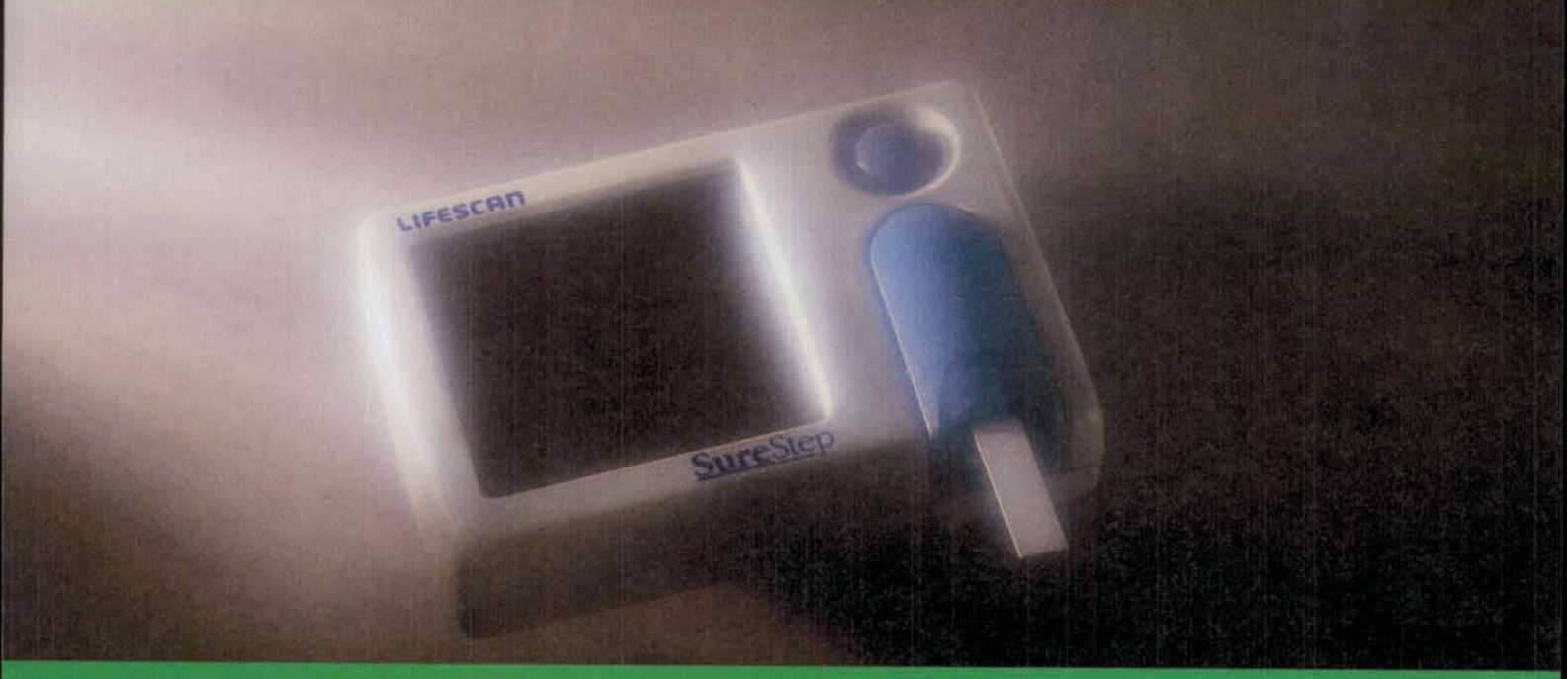
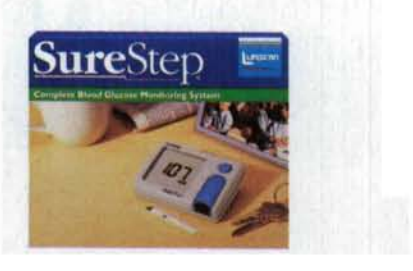
◆ Answers to frequently asked questions about diabetes
◆ Communicating with your health care provider
◆ Getting the most from your health care appointments
◆ Getting support
• talking to others
• organizations
◆ Description of Precose and how it works
◆ What to expect when taking Precose
◆ Tips on taking Precose
◆ Provide your name and address to request a Precose booklet
50 mg, 100 mg
Precose
(acarbose tablets)
Please see brief summary of prescribing information on adjacent page.



We take diabetes very personally.

Because diabetes affects everyone differently, it's important that the meter you recommend matches your patients' personal needs. Take the SureStep® Blood Glucose Monitoring System, for example. It's specially designed for patients who have difficulty testing and who want to be sure at every step. Blood application is easy because patients can actually touch the test strip with their finger. And the dot on the back turns blue, so they know that they've applied enough blood.

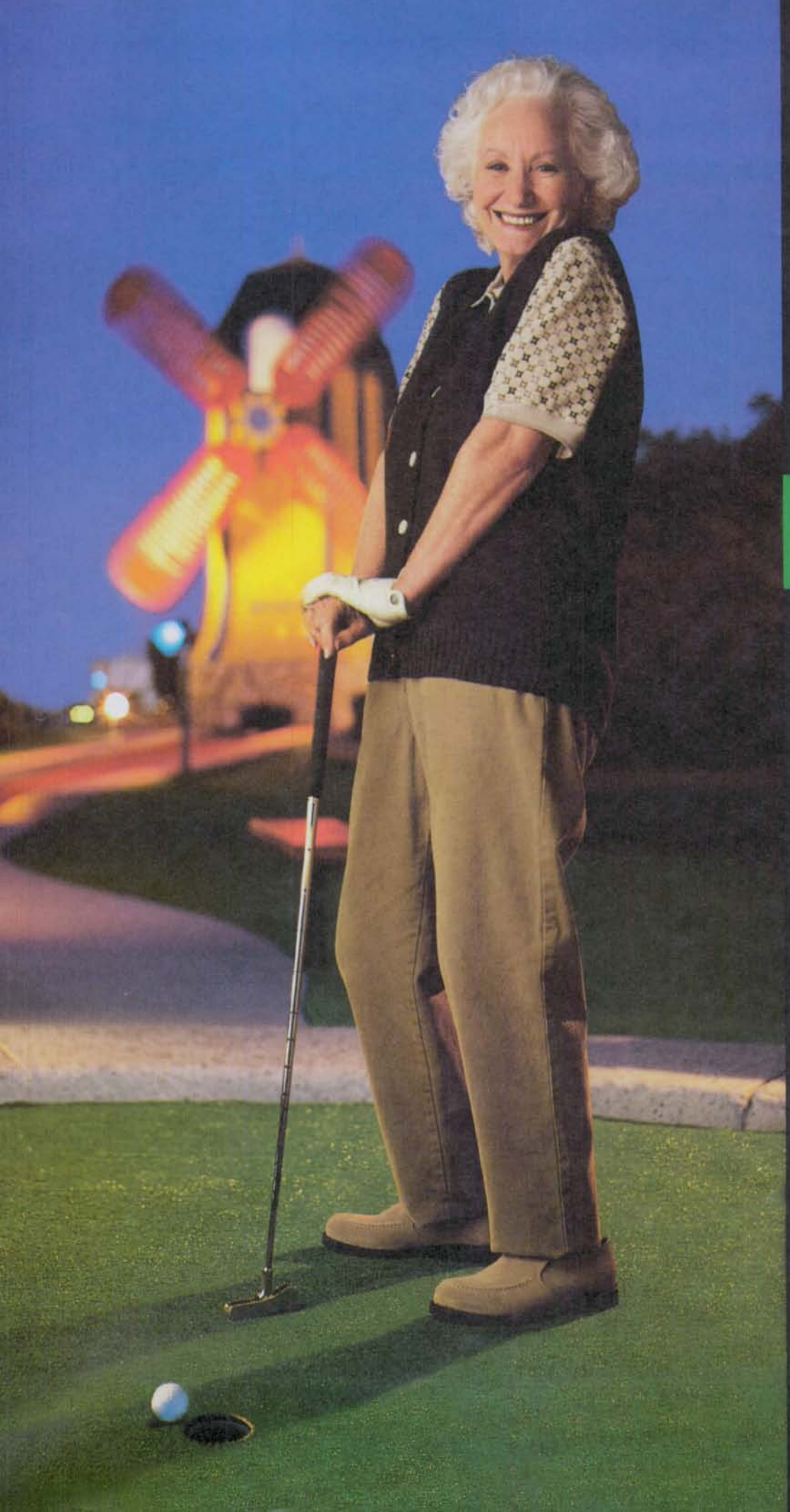
Make it your personal recommendation. The SureStep® System. The reassuring choice from LifeScan—makers of ONE TOUCH® Brand, the brand recommended by more healthcare professionals.



SureStep®
Blood Glucose Monitoring System

For diabetes and life.

LIFESCAN INC
a Johnson & Johnson company



"I have arthritis. So when I want to test, I use the SureStep® System. Its touchable test strip provides me with a target I just can't miss."

GLYCATED PROTEIN

The Gold Standard For Monitoring Glycemic Control

The NIH-sponsored Diabetes Control and Complications Trial (DCCT) proved conclusively that tight control of blood glucose can reduce the risk of diabetes complications. In the course of this study and other work, glycated protein testing has become recognized as the "gold standard" for measuring overall glycemic control.[1]

- Glycated protein tests can reliably indicate chronic hyperglycemia, the major risk factor for diabetes complications.[2]
- Glycated protein tests can be used to assess the results of a glucose self-testing regimen, they can indicate whether a treatment plan is working, and they can show how lifestyle choices can make a difference in diabetes control.
- Knowledge of glycated protein levels has been shown to affect beneficial changes in diabetes treatment and to result in improved glycemic control.[3]
- Some glycated protein tests are clinically more responsive to changes in glycemic control than others and are better able to monitor rapid changes in therapy or patient behavior.[4]
- Glycated protein testing is an important adjunct to glucose self-testing. Whereas glucose testing helps guide medication management and other daily routines, regular glycated protein testing helps guide overall disease management decisions.
- The American Diabetes Association recommends regular glycated protein testing for all persons with diabetes, both insulin dependent and non-insulin dependent.[5]

For more information, contact a LXN Technical Service Representative. LXN Corporation is a leader in the development of new technology for improved glycated protein testing.

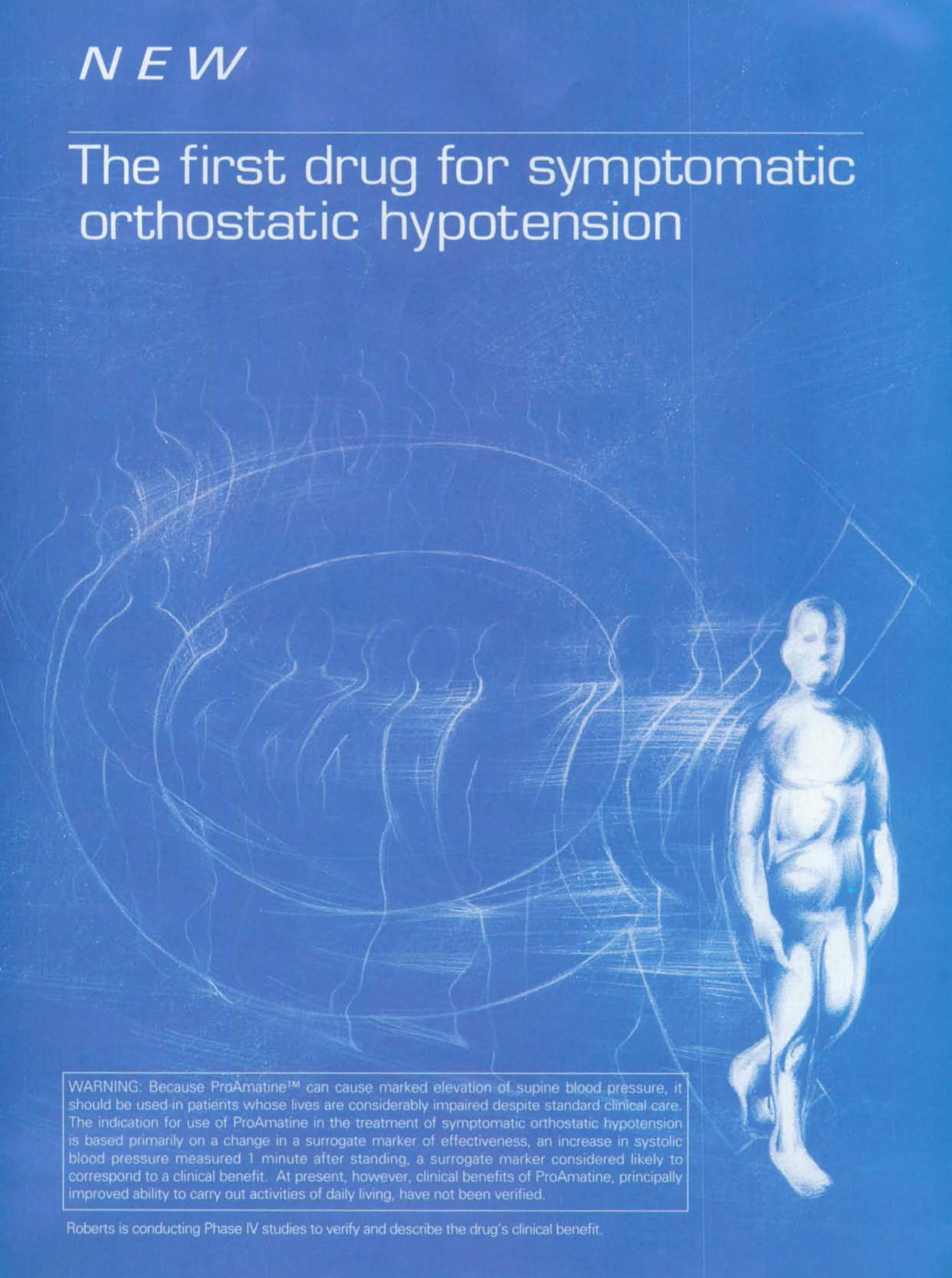
LXN Corporation

5830 Oberlin Drive, San Diego, CA 92121 1-888 LXN-TEST (596-8378)

5027-1

NEW

The first drug for symptomatic orthostatic hypotension



WARNING: Because ProAmatine™ can cause marked elevation of supine blood pressure, it should be used in patients whose lives are considerably impaired despite standard clinical care. The indication for use of ProAmatine in the treatment of symptomatic orthostatic hypotension is based primarily on a change in a surrogate marker of effectiveness, an increase in systolic blood pressure measured 1 minute after standing, a surrogate marker considered likely to correspond to a clinical benefit. At present, however, clinical benefits of ProAmatine, principally improved ability to carry out activities of daily living, have not been verified.

Roberts is conducting Phase IV studies to verify and describe the drug's clinical benefit.

NEW *Pharmacologic Support for Patients With*

ProAm (midodrine

Tablets of 2.5 mg and 5 mg

A unique alpha-adrenergic agent[1]

- Does not readily cross blood-brain barrier[1]
- Does not increase circulating volume[1]
- Duration of action ≈3 hours[3]

*Because ProAmatine can cause marked elevation of supine blood pressure, it should be used in patients whose lives are considerably impaired despite standard clinical care. ProAmatine should be used in patients who have not responded to standard clinical care such as support stockings, sleeping in the head-up tilt position, and increased salt intake.

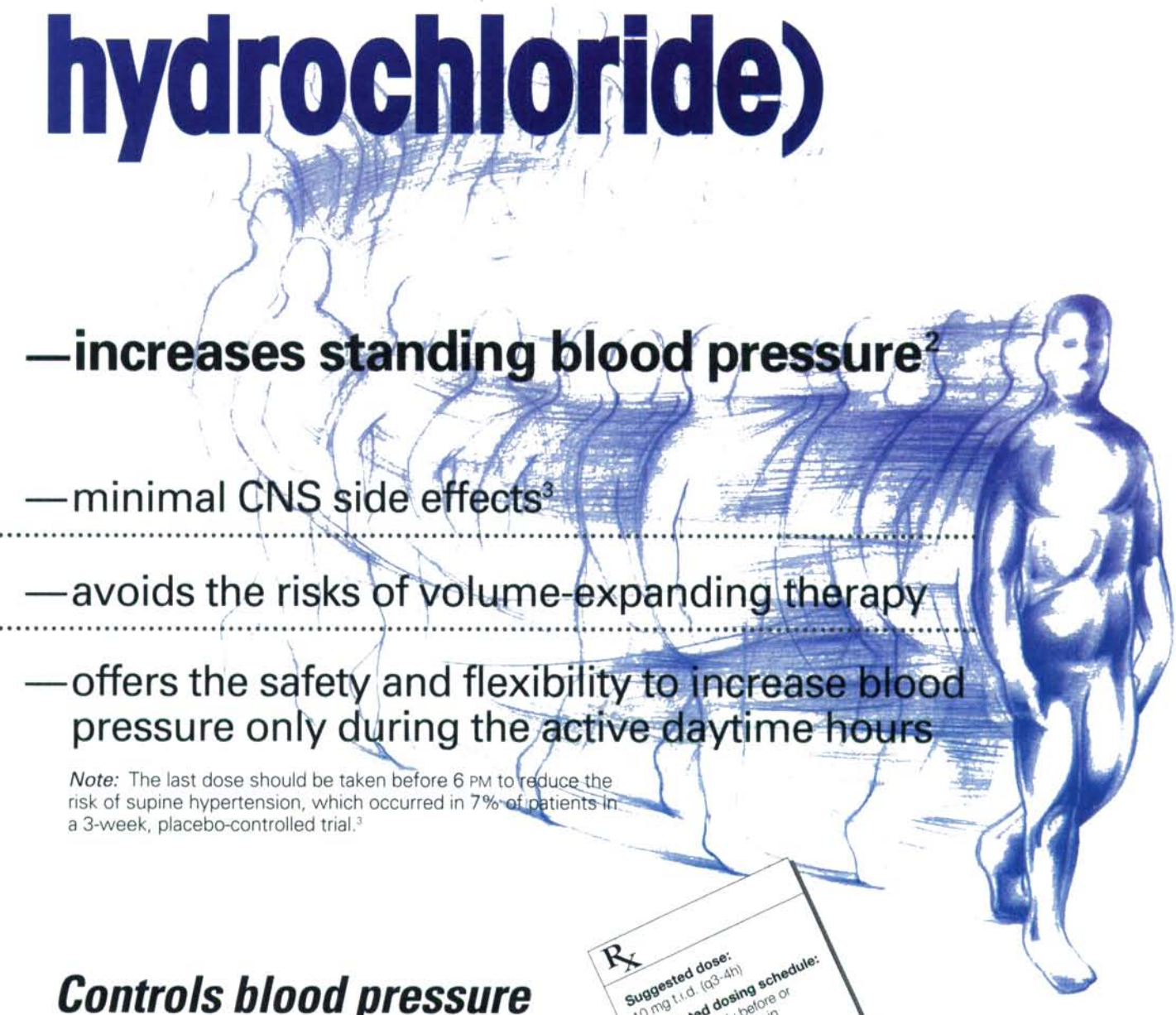
ProAmatine is contraindicated in patients with severe organic heart disease, acute renal disease, urinary retention, pheochromocytoma, or thyrotoxicosis and should not be used by patients with persistent and excessive supine hypertension.

See brief summary of full Prescribing Information on last page.

SYMPTOMS: DIZZINESS

*Symptomatic Orthostatic Hypotension (OH)**

atine™
hydrochloride)



—increases standing blood pressure[2]

—minimal CNS side effects[3]

—avoids the risks of volume-expanding therapy

—offers the safety and flexibility to increase blood pressure only during the active daytime hours

Note: The last dose should be taken before 6 PM to reduce the risk of supine hypertension, which occurred in 7% of patients in a 3-week, placebo-controlled trial.[3]

Controls blood pressure fall when your patients rise

SYNCOPE

ProAmatine®
(midodrine hydrochloride)

Tablets of 2.5 mg and 5 mg

Controls blood pressure fall when your patients rise

References: 1. McTavish D, Goa KL. Midodrine. A review of its pharmacological properties and therapeutic use in orthostatic hypotension and secondary hypotensive disorders. *Drugs*. 1989;38:757-777. 2. Data on file, Roberts Pharmaceutical Corporation. 3. Prescribing Information, ProAmatine®.

Brief Summary Consult the package insert for complete Prescribing Information.

WARNING: Because ProAmatine can cause marked elevation of supine blood pressure, it should be used in patients whose lives are considerably impaired despite standard clinical care. The indication for use of ProAmatine in the treatment of symptomatic orthostatic hypotension is based primarily on a change in a surrogate marker of effectiveness, an increase in systolic blood pressure measured one minute after standing, a surrogate marker considered likely to correspond to a clinical benefit. At present, however, clinical benefits of ProAmatine, principally improved ability to carry out activities of daily living, have not been verified.

Clinical Studies: Midodrine has been studied in 3 principal controlled trials, one of 3-weeks duration and 2 of 1 to 2 days duration. All studies were randomized, double-blind and parallel-design trials in patients with orthostatic hypotension of any etiology and supine-to-standing fall of systolic blood pressure of at least 15 mmHg accompanied by at least moderate dizziness/lightheadedness. Patients with pre-existing sustained supine hypertension above 180/110 mmHg were routinely excluded. In a 3-week study in 170 patients, most previously untreated with midodrine, the midodrine-treated patients (10 mg t.i.d., with the last dose not later than 6 P.M.) had significantly higher (by about 20 mmHg) 1-minute standing systolic pressure 1 hour after dosing (blood pressures were not measured at other times) for all 3 weeks. After week 1, midodrine-treated patients had small improvements in dizziness/lightheadedness/unsteadiness scores and global evaluations, but these effects were made difficult to interpret by a high early drop-out rate (about 25% vs 5% on placebo). Supine and sitting blood pressure rose 16/8 and 20/10 mmHg, respectively, on average. In a 2-day study, after open-label midodrine, known midodrine responders received midodrine 10 mg or placebo at 0, 3, and 6 hours. One-minute standing systolic blood pressures were increased 1 hour after each dose by about 15 mmHg and 3 hours after each dose by about 12 mmHg; 3-minute standing pressures were increased also at 1, but not 3, hours after dosing. There were increases in standing time seen intermittently 1 hour after dosing, but not at 3 hours. In a 1-day, dose-response trial, single doses of 0, 2.5, 10, and 20 mg of midodrine were given to 25 patients. The 10- and 20-mg doses produced increases in standing 1-minute systolic pressure of about 30 mmHg at 1 hour; the increase was sustained in part for 2 hours after 10 mg and 4 hours after 20 mg. Supine systolic pressure was ≥200 mmHg in 22% of patients on 10 mg and 45% of patients on 20 mg; elevated pressures often lasted 6 hours or more.

INDICATIONS AND USAGE: ProAmatine is indicated for the treatment of symptomatic orthostatic hypotension (OH). Because ProAmatine can cause marked elevation of supine blood pressure (BP>200 mmHg systolic), it should be used in patients whose lives are considerably impaired despite standard clinical care, including non-pharmacologic treatment (such as support stockings), fluid expansion, and lifestyle alterations. The indication is based on ProAmatine's effect on increases in 1-minute standing systolic blood pressure, a surrogate marker considered likely to correspond to a clinical benefit. At present, however, clinical benefits of ProAmatine, principally improved ability to perform life activities, have not been established. Further clinical trials are underway to verify and describe the clinical benefits of ProAmatine. After initiation of treatment, ProAmatine should be continued only for patients who report significant symptomatic improvement.

CONTRAINDICATIONS: ProAmatine is contraindicated in patients with severe organic heart disease, acute renal disease, urinary retention, pheochromocytoma or thyrotoxicosis. ProAmatine should not be used in patients with persistent and excessive supine hypertension.

WARNINGS: Supine Hypertension: The most potentially serious adverse reaction associated with ProAmatine therapy is marked elevation of supine arterial blood pressure (supine hypertension). Systolic pressure of about 200 mmHg were seen overall in about 13.4% of patients given 10 mg of ProAmatine. Systolic elevations of this degree were most likely to be observed in patients with relatively elevated pretreatment systolic blood pressures (mean 170 mmHg). There is no experience in patients with initial supine systolic pressure above 180 mmHg, as those patients were excluded from the clinical trials. Use of ProAmatine in such patients is not recommended. Sitting blood pressures were also elevated by ProAmatine therapy. It is essential to monitor supine and sitting blood pressures in patients maintained on ProAmatine.

PRECAUTIONS

General: The potential for supine and sitting hypertension should be evaluated at the beginning of ProAmatine therapy. Supine hypertension can often be controlled by preventing the patient from becoming fully supine, i.e., sleeping with the head of the bed elevated. The patient should be cautioned to report symptoms of supine hypertension immediately. Symptoms may include cardiac awareness, pounding in the ears, headache, blurred vision, etc. The patient should be advised to discontinue the medication immediately if supine hypertension persists. Blood pressure should be monitored carefully when ProAmatine is used concomitantly with other agents that cause vasoconstriction, such as phenylephrine, ephedrine, dihydroergotamine, phenylpropanolamine, or pseudoephedrine. A slight slowing of the heart rate may occur after administration of ProAmatine, primarily due to vagal reflex. Caution should be exercised when ProAmatine is used concomitantly with cardiac glycosides (such as digitalis), psychopharmacologic agents, beta blockers or other agents that directly or indirectly reduce heart rate. Patients who experience any signs or symptoms suggesting bradycardia (pulse slowing, increased dizziness, syncope, cardiac awareness) should be advised to discontinue ProAmatine and should be re-evaluated. ProAmatine should be used cautiously in patients with urinary retention problems, as desglymidodrine acts on the alpha-adrenergic receptors of the bladder neck. ProAmatine should be used with caution in orthostatic hypotensive patients who are also diabetic, as well as those with a history of visual problems who are also taking fludrocortisone acetate, which is known to cause an increase in intraocular pressure and glaucoma. ProAmatine use has not been studied in patients with renal impairment. Because desglymidodrine is eliminated via the kidneys, and higher blood levels would be expected in such patients, ProAmatine should be used with caution in patients with renal impairment, with a starting dose of 2.5 mg (see **DOSAGE AND ADMINISTRATION**). Renal function should be assessed prior to initial use of ProAmatine. ProAmatine use has not been studied in patients with hepatic impairment. ProAmatine should be used with caution in patients with hepatic impairment, as the liver has a role in the metabolism of midodrine.

Information for Patients: Patients should be told that certain agents in over-the-counter products, such as cold remedies and diet aids, can elevate blood pressure, and therefore, should be used cautiously with ProAmatine, as they may enhance or potentiate the pressor effects of ProAmatine (see **Drug Interactions**). Patients should also be made aware of the possibility of supine hypertension. They should be told to avoid taking their dose if they are to be supine for any length of time, i.e., they should take their last daily dose of ProAmatine 3 to 4 hours before bedtime to minimize nighttime supine hypertension.

Laboratory Tests: Since desglymidodrine is eliminated by the kidneys and the liver has a role in its metabolism, evaluation of the patient should include assessment of renal and hepatic function prior to initiating therapy and subsequently, as appropriate.

Drug Interactions: When administered concomitantly with ProAmatine, cardiac glycosides may enhance or precipitate bradycardia, A.V. block or arrhythmia. The use of drugs that stimulate alpha-adrenergic receptors (e.g., phenylephrine, pseudoephedrine, ephedrine, phenylpropanolamine or dihydroergotamine) may enhance or potentiate the pressor effects of ProAmatine. Therefore, caution should be used when ProAmatine is administered concomitantly with agents that cause vasoconstriction. ProAmatine has been used in patients concomitantly treated with salt-retaining steroid therapy (i.e., fludrocortisone acetate), with or without salt supplementation. The potential for supine hypertension should be carefully monitored in these patients and may be minimized by either reducing the dose of fludrocortisone acetate or decreasing the salt intake prior to initiation of treatment with ProAmatine. Alpha-adrenergic blocking agents, such as prazosin, terazosin, and doxazosin, can antagonize the effects of ProAmatine.

Potential for Drug Interactions: It appears possible, although there is no supporting experimental evidence, that the high renal clearance of desglymidodrine (a base) is due to active tubular secretion by the base-secreting system also responsible for the secretion of such drugs as metformin, cimetidine, ranitidine, procainamide, triamterene, flecainide, and quinidine. Thus there may be a potential for drug-drug interactions with these drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies have been conducted in rats and mice at dosages of 3 to 4 times the maximum recommended daily human dose on a mg/m² basis, with no indication of carcinogenic effects related to ProAmatine. Studies investigating the mutagenic potential of ProAmatine revealed no evidence of mutagenicity. Other than the dominant lethal assay in male mice, where no impairment of fertility was observed, there have been no studies on the effects of ProAmatine on fertility.

Pregnancy: *Pregnancy Category C.* ProAmatine increased the rate of embryo resorption, reduced fetal body weight in rats and rabbits, and decreased fetal survival in rabbits when given in doses 13 (rat) and 7 (rabbit) times the maximum human dose based on body surface area (mg/m²). There are no adequate and well-controlled studies in pregnant women. ProAmatine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No teratogenic effects have been observed in studies in rats and rabbits.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ProAmatine is administered to a nursing woman.

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

ADVERSE REACTIONS: The most frequent adverse reactions seen in controlled trials were supine and sitting hypertension; paresthesia and pruritus, mainly of the scalp; goosebumps; chills; urinary urge; urinary retention and urinary frequency.

The frequency of these events in a 3-week placebo-controlled trial is shown in the following table:

Adverse Events

	Placebo (n=88)		Midodrine (n=82)	
Event	# of reports	% of patients	# of reports	% of patients
Total # of reports	22		77	
Paresthesia[1]	4	4.5	15	18.3
Piloerection	0	0	11	13.4
Dysuria[2]	0	0	11	13.4
Pruritus[3]	2	2.3	10	12.2
Supine hypertension[4]	0	0	6	7.3
Chills	0	0	4	4.9
Pain[5]	0	0	4	4.9
Rash	1	1.1	2	2.4

1 Includes hyperesthesia and scalp paresthesia
2 Includes dysuria (1), increased urinary frequency (2), impaired urination (1), urinary retention (5), urinary urgency (2)
3 Includes scalp pruritus
4 Includes patients who experienced an increase in supine hypertension
5 Includes abdominal pain and pain increase

Less frequent adverse reactions were headache; feeling of pressure/fullness in the head; vasodilation/flushing face; confusion/thinking abnormality; dry mouth; nervousness/anxiety and rash. Other adverse reactions that occurred rarely were visual field defect; dizziness; skin hyperesthesia; insomnia; somnolence; erythema multiforme; canker sore; dry skin; dysuria; impaired urination; asthenia; backache; pyrosis; nausea; gastrointestinal distress; flatulence and leg cramps. The most potentially serious adverse reaction associated with ProAmatine therapy is supine hypertension. The feelings of paresthesia, pruritus, piloerection and chills are pilomotor reactions associated with the action of midodrine on the alpha-adrenergic receptors of the hair follicles. Feelings of urinary urgency, retention and frequency are associated with the action of midodrine on the alpha-receptors of the bladder neck.

OVERDOSAGE: Symptoms of overdose could include hypertension, piloerection (goosebumps), a sensation of coldness and urinary retention. There are 2 reported cases of overdosage with ProAmatine, both in young males. One patient ingested ProAmatine drops, 250 mg, experienced systolic blood pressure of greater than 200 mmHg, was treated with an IV injection of 20 mg of phentolamine, and was discharged the same night without any complaints. The other patient ingested 205 mg of ProAmatine (41 5-mg tablets), and was found lethargic and unable to talk, unresponsive to voice but responsive to painful stimuli, hypertensive and bradycardic. Gastric lavage was performed, and the patient recovered fully by the next day without sequelae. The single doses that would be associated with symptoms of overdosage or would be potentially life-threatening are unknown. The oral LD_{50} is approximately 30 to 50 mg/kg in rats, 675 mg/kg in mice, and 125 to 160 mg/kg in dogs. Desglymidodrine is dialyzable. Recommended general treatment, based on the pharmacology of the drug, includes induced emesis and administration of alpha-sympatholytic drugs (e.g., phentolamine).

DOSAGE AND ADMINISTRATION: The recommended dose of ProAmatine is 10 mg, 3 times daily. Dosing should take place during the daytime hours when the patient needs to be upright, pursuing the activities of daily life. A suggested dosing schedule of approximately 4-hour intervals is as follows: shortly before or upon arising in the morning, midday, and late afternoon (not later than 6 P.M.). Doses may be given in 3-hour intervals, if required, to control symptoms, but not more frequently. Single doses as high as 20 mg have been given to patients, but severe and persistent systolic supine hypertension occur at a high rate (about 45%) at this dose. In order to reduce the potential for supine hypertension during sleep, ProAmatine should not be given after the evening meal or less than 4 hours before bedtime. Total daily doses greater than 30 mg have been tolerated by some patients, but their safety and usefulness have not been studied systematically or established. Because of the risk of supine hypertension, ProAmatine should be continued only in patients who appear to attain symptomatic improvement during initial treatment. The supine and standing blood pressure should be monitored regularly, and the administration of ProAmatine should be stopped if supine blood pressure increases excessively. Because desglymidodrine is excreted renally, dosing in patients with abnormal renal function should be cautious; although this has not been systematically studied, it is recommended that treatment of these patients be initiated using 2.5-mg doses. Dosing in children has not been adequately studied. Blood levels of midodrine and desglymidodrine were similar when comparing levels in patients 65 or older vs. younger than 65 and when comparing males vs. females, suggesting dose modifications for these groups are not necessary.

HOW SUPPLIED: ProAmatine is supplied as 2.5-mg and 5-mg tablets for oral administration. The 2.5-mg tablet is white, round, and biplanar, with a bevelled edge, and is scored on 1 side with "RPC" above and "2.5" below the score, and "003" on the other side. The 5-mg tablet is orange, round, and biplanar, with a bevelled edge, and is scored on 1 side with "RPC" above and "5" below the score, and "004" on the other side.

2.5-milligram Tablets:	NDC 54092-003-01	Bottle of 100
5-milligram Tablets:	NDC 54092-004-01	Bottle of 100

Store from 15°C to 25°C (59°F to 77°F).
CAUTION: Keep this and all medication out of the reach of children.

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ATHEROGENESIS IN DIABETES:
The Clinical Benefits of Lipid Lowering Therapy

Sponsored by Baylor College of Medicine, Houston, Texas

The John B. Hynes Convention Center ◆ Ballroom B
900 Boylston Street ◆ Boston, Massachusetts

Friday, June 20, 1997

5:30 PM to 6:00 PM: **Registration and Hors d'Oeuvres**
6:00 PM to 8:00 PM: **Symposium**
8:00 PM: **"Meet the Faculty" Dinner Reception**

Program Director

Alan J. Garber, MD, PhD
Professor of Medicine, Biochemistry and Cell Biology
Baylor College of Medicine
Chief of Endocrinology, Diabetes and Metabolism
The Methodist Hospital
Houston, Texas

6:00 PM Opening Remarks and Welcome
Alan J. Garber, MD, PhD

The Atherogenic Profile in Diabetes:
The Reemerging Importance of LDL Cholesterol
Alan J. Garber, MD, PhD

Cardiovascular Disease in Diabetes:
Perspectives from the NCEP
Henry N. Ginsberg, MD

CHD Risk Reduction in Diabetes:
The New Age of Statin Therapy
Stephen R. Crespin, MD

Interventional and Postinterventional Management of CVD:
Implications of the BARI and Post-CABG Trials
Donald B. Hunninghake, MD

Interactive Question-and-Answer/Discussion Session
Moderator: Alan J. Garber, MD, PhD
Faculty Panel

8:00 PM Closing Remarks
Alan J. Garber, MD, PhD

Registration Information

Advanced registration is requested; there will be no charge. Registration is confirmed unless you are otherwise notified. To register by phone, call the conference coordinator, SynerMed, at 908.832.4142, or fax at 908.832.9083. On-site registration will be available as space allows.

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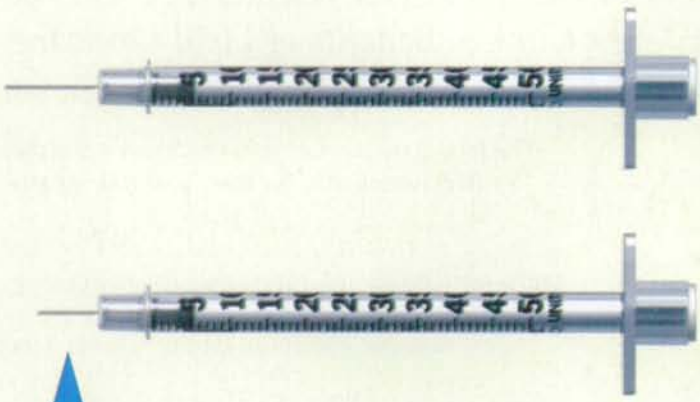

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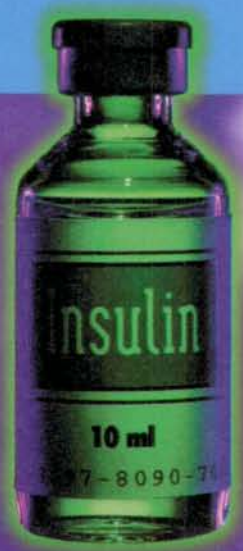

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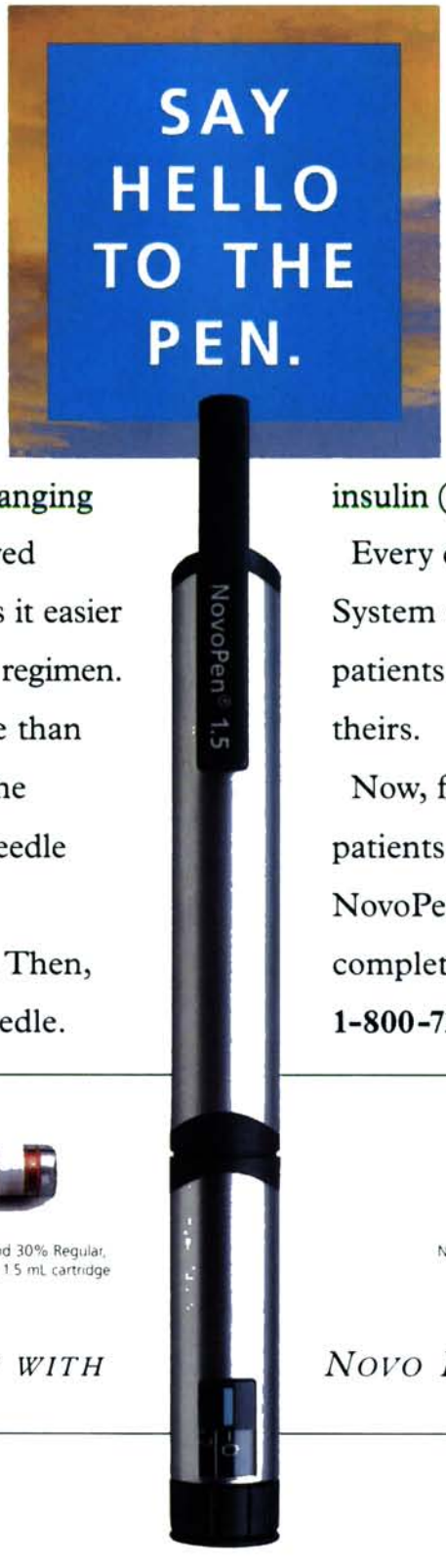

Push the button.

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70% NPH, Human Insulin Isophane Suspension and 30% Regular, Human Insulin Injection (recombinant DNA origin), 1.5 mL cartridge

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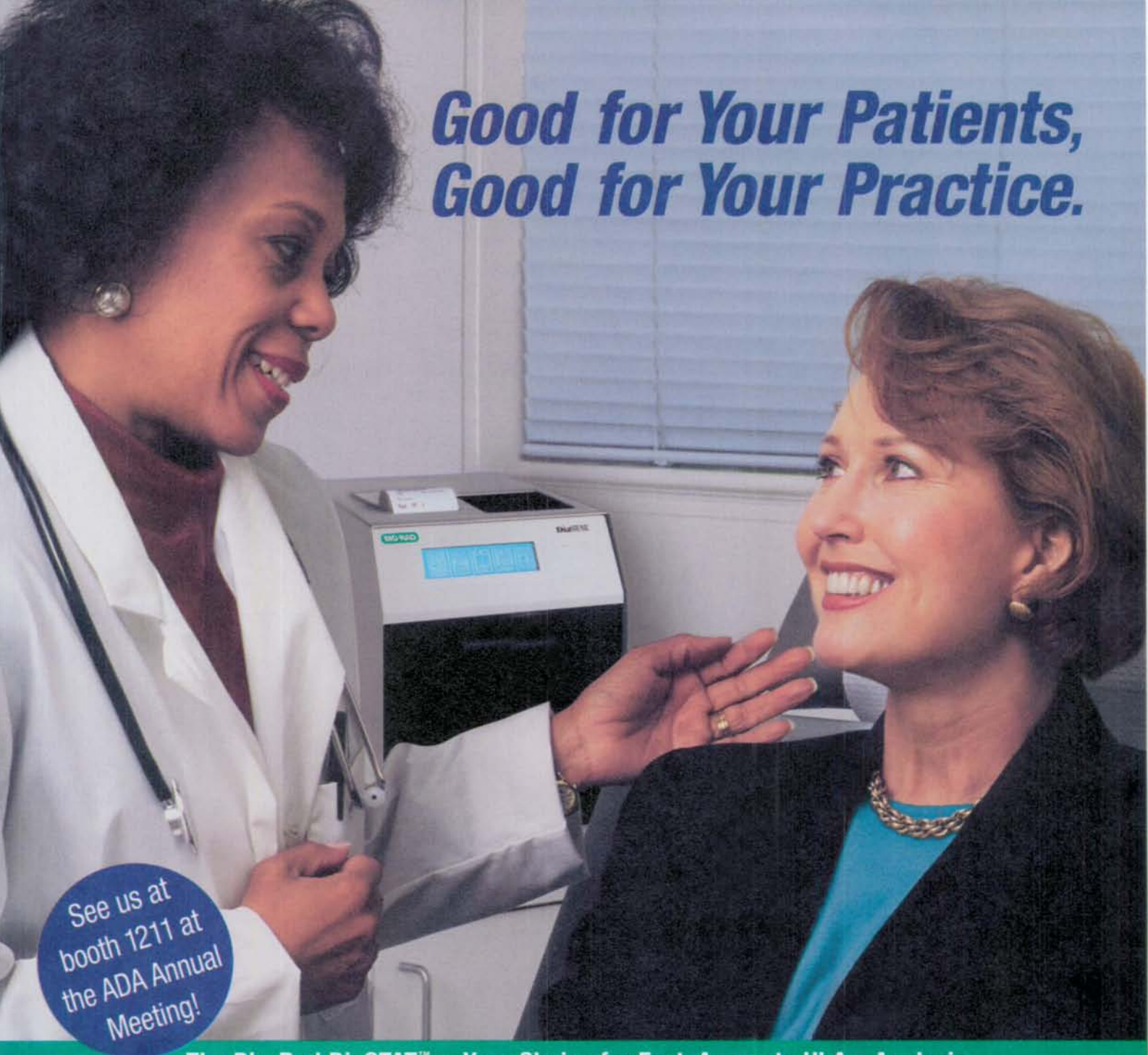

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ArtAssist® Case Report

Diabetic limb salvage using the Arterial Assist Device. . . ArtAssist*

Paul S. van Bemmelen, MD, PhD, Port Jefferson, NY and
Gerald J. Furst, DPM, Port Jefferson, NY

Patient

- 66 Year Old Male
- 35 Year Hx of Diabetes
- Renal Failure
- Contralateral Tibial Bypass
- Poor Ambulation
- Small Vessel Disease

Past Therapies

- Amputation Great Toe/Metatarsal I
- Platelet Released Growth Factors
- IV and Oral Antibiotics
- Topical Antibiotics
- Surgical Debridements

ArtAssist® Device

- Applies Compression to Foot, Ankle and Calf Up to 100 mmHg
- Home use for 30 min. QID
- Well Tolerated on Sitting Patient
- Improved Circulation
- Prepared Foot For Revision Surgery

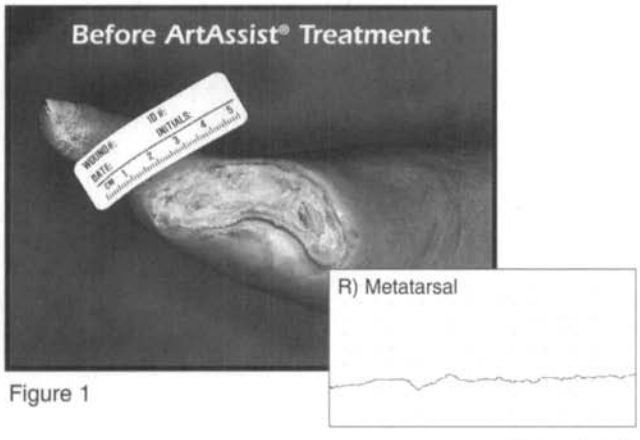

Figure 1

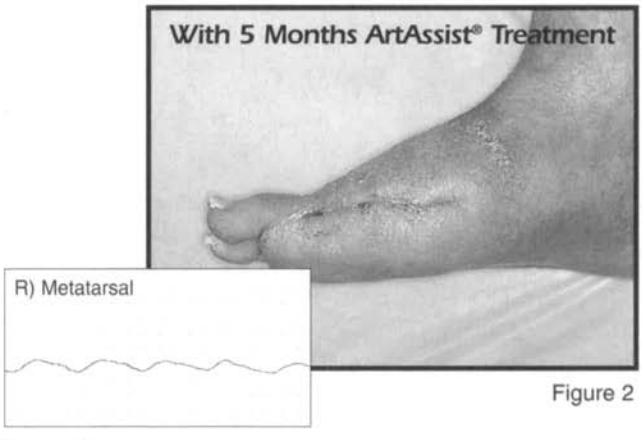

Figure 2

Pulse Volume Recordings

A 66 year old man with a 35 year history of diabetes (NIDDM) and chronic renal failure (peritoneal dialysis) presented with dry necrosis of his right great toe. He ambulated very little outside of his home and he had previously undergone a tibial bypass of the opposite leg. He was being treated with platelet released growth factors for poor healing of his left distal ankle incision. Ankle blood pressure was not obtainable due to non-compressibility, but wave forms were consistent with disease of the small vessels distal to the knee. The metatarsal pulse volume recording† is shown (Fig. 1) and is essentially flat. Toe-pressure was in the ischemic range.

The patient underwent repeated selective digital intra-arterial angiography, which demonstrated patent arteries to the level of the ankle only, without named run-off vessels in the foot. After explaining the poor chances of healing of a toe amputation to the patient, he underwent amputation of the right great toe and metatarsal head. Treatment with the ArtAssist device was not available at that time. The toe amputation failed and complete dehiscence, with exposed metatarsal bone was apparent in (Fig.1). Debridements and immediate treatment with growth factors were instituted. Further deterioration occurred slowly. Further revision foot amputation was not considered to be a worthwhile option and below-knee amputation would be the next surgical step.

Intermittent compression with the ArtAssist device was started two months after the toe amputation for at least 30 minutes, QID. Compression was well tolerated and after one week of home treatment, the patient noticed blood on his dressings. Slowly some granulation tissue appeared and the wound edges bled well with minor debridements. Improvement of the metatarsal pulse volume recording was noted. In view of the exposed metatarsal bone, with retracted skin edges, a further resection of Metatarsal I and the adjacent second toe was performed after two months of compression therapy. Oral antibiotics were given based on culture results. The growth factor treatment was stopped. The resulting wound is now healed by secondary intention (Fig.2). Further improvements occurred of the pulse volume recording at the metatarsal level, to the same amplitude as the bypassed side.

† Parks Flow-Lab

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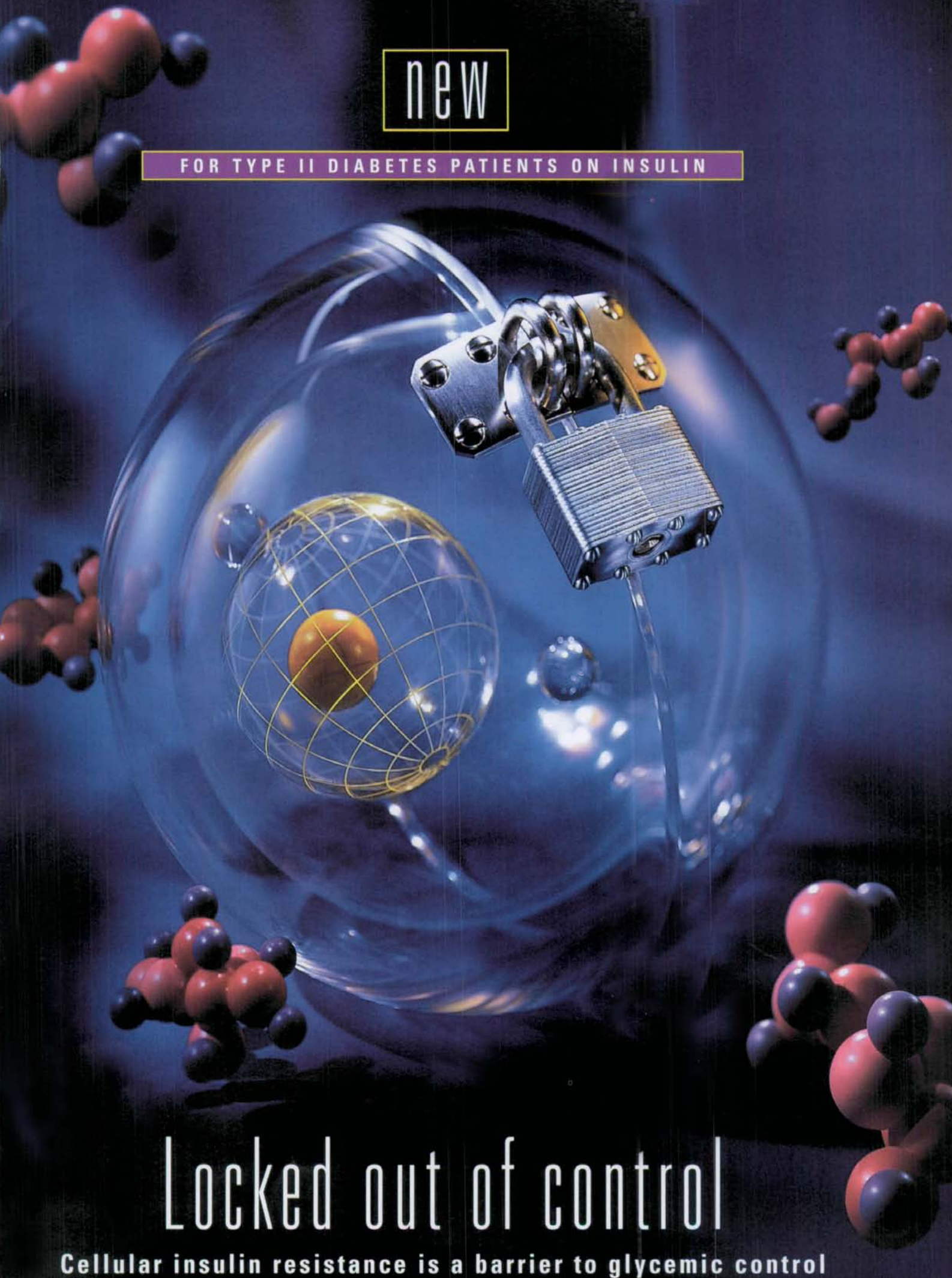
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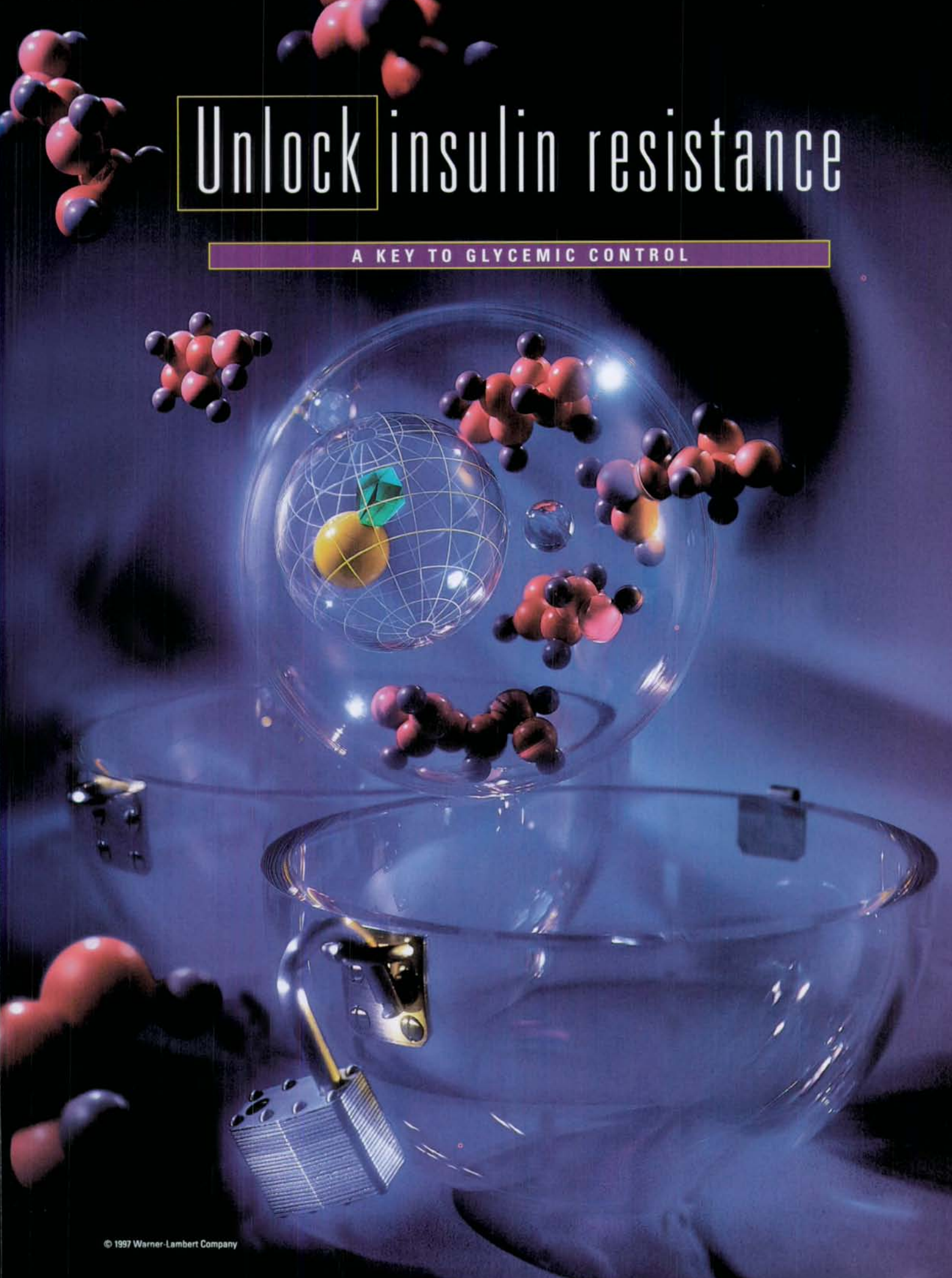

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In clinical trials, consistent improvement in control[1]

- Significantly lowers fasting serum glucose and glycosylated hemoglobin (HbA_{1c})
- Reduces or eliminates the need for exogenous insulin to maintain glycemic control
- May reduce the frequency of insulin injections

Excellent safety and tolerability profile

- Side effects comparable to placebo in clinical trials. The most common side effects were infection (22% placebo vs 18% Rezulin group), headache (11% placebo vs 11% Rezulin group), and pain (14% placebo vs 10% Rezulin group)
- Hypoglycemia has not been observed during the administration of Rezulin as monotherapy. Patients receiving Rezulin in combination with insulin may be at risk for hypoglycemia, and a reduction in the dose of insulin may be necessary
- Rezulin should be used with caution in patients with hepatic dysfunction
- No dose adjustment in patients with renal dysfunction

The clinical effects of Rezulin occur independent of weight loss

FOR TYPE II DIABETES PATIENTS ON INSULIN

new REZULIN™

Unlocks insulin resistance

Prior to initiation of Rezulin therapy, correctable causes of poor glycemic control should be sought and treated.

Rezulin should not be used in Type I diabetes or for the treatment of diabetic ketoacidosis.

Rezulin has not been tested in patients with New York Heart Association (NYHA) Class III and IV cardiac status; therefore, caution is advised in administering Rezulin to these patients.

Management of Type II diabetes should also include diet control, weight loss, and exercise.

Reference: 1. Data on file, Parke-Davis.

Please see Brief Summary of Prescribing Information on last page of this advertisement.

new

ONCE-DAILY

REZULIN™

TROGLITAZONE

200, 400 MG TABLETS

UNLOCKS INSULIN RESISTANCE

BRIEF SUMMARY

Consult Package Insert for full Prescribing Information.

INDICATIONS AND USAGE

Rezulin is indicated for use in patients with type II diabetes currently on insulin therapy whose hyperglycemia is inadequately controlled (HbA_{1C} >8.5%) despite insulin therapy of over 30 units per day given as multiple injections.

Management of type II diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient. This is important not only in the primary treatment of type II diabetes, but in maintaining the efficacy of drug therapy. Prior to initiation of Rezulin therapy, secondary causes of poor glycemic control, eg, infection or poor injection technique, should be investigated and treated.

CONTRAINDICATIONS

Rezulin is contraindicated in patients with known hypersensitivity or allergy to Rezulin or any of its components.

PRECAUTIONS

General

Because of its mechanism of action, Rezulin is active only in the presence of insulin. Therefore, Rezulin should not be used in type I diabetes or for the treatment of diabetic keto-acidosis.

Hepatic: During all clinical studies in North America (N=2510 patients), a total of 20 Rezulin-treated patients were withdrawn from treatment because of liver function test abnormalities. Two of the 20 patients developed reversible jaundice. Both had liver biopsies which were consistent with an idiosyncratic drug reaction (see ADVERSE REACTIONS, Laboratory Abnormalities).

Hypoglycemia: Patients receiving Rezulin in combination with insulin may be at risk for hypoglycemia and a reduction in the dose of insulin may be necessary. Hypoglycemia has not been observed during the administration of Rezulin as monotherapy and would not be expected based on the mechanism of action.

Ovulation: In premenopausal anovulatory patients with insulin resistance, Rezulin treatment may result in resumption of ovulation. **These patients may be at risk for pregnancy.**

Hematologic: Across all clinical studies, hemoglobin declined by 3 to 4% in troglitazone-treated patients compared with 1 to 2% in those treated with placebo. White blood cell counts also declined slightly in troglitazone-treated patients compared to those treated with placebo. These changes occurred within the first four to eight weeks of therapy. Levels stabilized and remained unchanged for up to two years of continuing therapy. These changes may be due to the dilutional effects of increased plasma volume and have not been associated with any significant hematologic clinical effects (See ADVERSE REACTIONS, Laboratory Abnormalities).

Information for Patients

Rezulin should be taken with meals. If the dose is missed at the usual meal, it may be taken at the next meal. If the dose is missed on one day, the dose should not be doubled the following day.

It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. During periods of stress such as fever, trauma, infection, or surgery, insulin requirements may change and patients should seek the advice of their physician.

When using combination therapy with insulin, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Drug Interactions

Cholestyramine: Concomitant administration of cholestyramine with Rezulin reduces the absorption of troglitazone by approximately 70%; thus, coadministration of cholestyramine and Rezulin is not recommended.

Acetaminophen: Coadministration of acetaminophen and Rezulin does not alter the pharmacokinetics of either drug.

Warfarin: Rezulin has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Sulfonylureas: Coadministration of Rezulin with glyburide does not appear to alter troglitazone or glyburide pharmacokinetics, but may further decrease fasting plasma glucose. There are insufficient data on the use of Rezulin with sulfonylureas to establish the efficacy of this combination.

Metformin: No information is available on the use of Rezulin with metformin.

Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in Rezulin-treated patients with type II diabetes mellitus.

Terfenadine: Coadministration of Rezulin with terfenadine decreases plasma concentrations of terfenadine and its active metabolite by 50 to 70% and may reduce the effectiveness of terfenadine.

Oral Contraceptives: Administration of Rezulin with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%. These changes could result in loss of contraception. The above interactions with terfenadine and oral contraceptives suggest that troglitazone may induce drug metabolism by CYP3A4. These findings should be considered when prescribing other CYP3A4 substrates such as cyclosporine, tacrolimus and some HMG-CoA reductase inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Troglitazone was administered daily for 104 weeks to male rats at 100, 400, or 800 mg/kg and to female rats at 25, 50, or 200 mg/kg. Maximum plasma troglitazone AUC values based on parent compound represent exposures 12- and 47-fold higher for male and female rats, respectively, than human exposure of 400 mg daily. Troglitazone was not carcinogenic in male rats at any dose tested. In female rats, there was a statistically significant increase in sarcomatous tumors at the high dose (47-fold greater than estimated human exposure of parent compound). However, these findings are of unknown clinical relevance as this dose was associated with excessive mortality and is considered to have surpassed the maximum tolerated dose. No tumors of any type were increased in rats at 25 and 50 mg/kg at exposures of 5- to 14-fold higher than in humans based on AUC of parent compound. In a 104-week study in mice given 50, 400, or 800 mg/kg, incidence of hemangiosarcoma was increased in females at 400 mg/kg and in both sexes at 800 mg/kg; incidence of hepatocellular carcinoma was increased in females at 800 mg/kg. The lowest dose with increased tumor incidence (400 mg/kg) was associated with AUC values of parent compound that were at least 16-fold higher than the human exposure. No tumors of any type were increased in mice at 50 mg/kg at exposures 2- to 4-fold higher than in humans based on AUC of parent compound.

Troglitazone was neither mutagenic in bacteria nor clastogenic in bone marrow of mice. Equivocal increases in chromosome aberrations were observed in an *in vitro* Chinese hamster lung cell assay. In mouse lymphoma cell gene mutations assays, results were equivocal when conducted with a microtiter technique and negative with an agar plate technique. A liver unscheduled DNA synthesis assay in rats was negative.

No adverse effects on fertility or reproduction were observed in male or female rats given 40, 200, or 1000 mg/kg daily prior to and throughout mating and gestation. AUC at these doses was estimated to be 2- to 8-fold higher than the human exposure.

Pregnancy

Pregnancy Category B. Troglitazone was not teratogenic in rats given up to 2000 mg/kg or rabbits given up to 1000 mg/kg during organogenesis. Compared to human exposure of 400 mg daily, estimated exposures based on AUC at these doses were up to 8-fold higher in rats and up to 6-fold higher in rabbits. Body weights of fetuses and offspring of rats given 2000 mg/kg during gestation were decreased. Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats given 40, 200, or 1000 mg/kg during late gestation and lactation periods; no effects were observed in offspring of rats given 10 or 20 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Rezulin should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers

It is not known whether troglitazone is secreted in human milk. Troglitazone is secreted in the milk of lactating rats. Because many drugs are excreted in human milk, Rezulin should not be administered to a breast-feeding woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

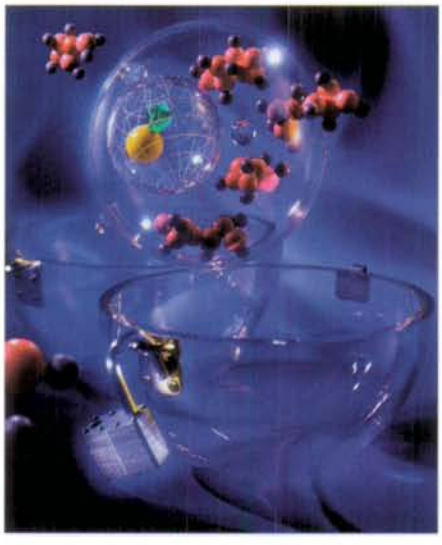
Twenty-two percent of patients in clinical trials of Rezulin were 65 and over. No differences in effectiveness and safety were observed between these patients and younger patients.

Use in Patients With Heart Failure

Heart enlargement without microscopic changes has been observed in rodents at exposures exceeding 14 times the AUC of the 400 mg human dose. Serial echocardiographic evaluations in monkeys treated chronically at maximum achievable exposures (3-5 times the human exposure at the 400 mg dose) did not reveal changes in heart size or function. In a 2-year echocardiographic clinical study using 600 to 800 mg/day of Rezulin in patients with type II diabetes, no increase in left ventricular mass or decrease in cardiac output was observed. The methodology employed was able to detect a change of about 10% or more in left ventricular mass.

In animal studies, troglitazone treatment was associated with increases of 6% to 15% in plasma volume. In a study of 24 normal volunteers, an increase in plasma volume of 6% to 8% compared to placebo was observed following 6 weeks of troglitazone treatment.

No increased incidence of adverse events potentially related to volume expansion (eg, congestive heart failure) have been observed during controlled clinical trials. However, patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during clinical trials. Therefore, caution is advised during the administration of Rezulin to patients with NYHA Class III or IV cardiac status.



ADVERSE REACTIONS

In general, Rezulin is well-tolerated. Two patients in the clinical studies developed reversible jaundice with findings on liver biopsy consistent with idiosyncratic drug reaction (See PRECAUTIONS, General).

The overall incidence and types of adverse reactions reported in placebo-controlled clinical trials for Rezulin-treated patients and placebo-treated patients are shown in Table 1. In patients treated with Rezulin in glyburide-controlled studies (N=550) or uncontrolled studies (N=510), the safety profile of Rezulin appeared similar to that displayed in Table 1. The incidence of withdrawals during clinical trials was similar for patients treated with placebo or Rezulin (4%).

TABLE 1. North American Placebo-Controlled Clinical Studies: Adverse Events Reported at a Frequency ≥ 5% of Rezulin-Treated Patients (% of Patients)

	Placebo N = 492	Rezulin N = 1450
Infection	22	18
Headache	11	11
Pain	14	10
Accidental Injury	6	8
Asthenia	5	6
Dizziness	5	6
Back Pain	4	6
Nausea	4	6
Rhinitis	7	5
Diarrhea	6	5
Urinary Tract Infection	6	5
Peripheral Edema	5	5
Pharyngitis	4	5

Types of adverse events seen when Rezulin was used concomitantly with insulin (N=543) were similar to those during Rezulin monotherapy (N=1731), although hypoglycemia occurred on insulin combination therapy (see PRECAUTIONS).

Laboratory Abnormalities

Hematologic: Small decreases in hemoglobin, hematocrit, and neutrophil counts (within the normal range) were more common in Rezulin-treated than placebo-treated patients and may be related to increased plasma volume observed with Rezulin treatment. Hemoglobin decreases to below the normal range occurred in 5% of Rezulin-treated and 4% of placebo-treated patients.

Lipids: Small changes in serum lipids have been observed (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects in package insert for full prescribing information).

Serum Transaminase Levels: During controlled clinical trials, 2.2% of Rezulin-treated patients had reversible elevations in AST or ALT greater than 3 times the upper limit of normal, compared with 0.6% of patients receiving placebo. Hyperbilirubinemia (>1.25 upper limit of normal) was found in 0.7% of Rezulin-treated patients compared with 1.7% of patients receiving placebo. In the population of patients treated with Rezulin, mean and median values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline, while values for LDH were increased slightly (see PRECAUTIONS, General, Hepatic).

DOSAGE AND ADMINISTRATION

The current insulin dose should be continued upon initiation of Rezulin therapy. Rezulin therapy should be initiated at 200 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of Rezulin should be increased after approximately 2 to 4 weeks. The usual dose of Rezulin is 400 mg once daily. The maximum recommended daily dose is 600 mg. It is recommended that the insulin dose be decreased by 10% to 25% when fasting plasma glucose concentrations decrease to less than 120 mg/dL in patients receiving concomitant insulin and Rezulin. Further adjustments should be individualized based on glucose-lowering response. Rezulin should be taken with a meal.

Patients With Renal Insufficiency

Dose adjustment in patients with renal insufficiency is not required (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism in package insert for full prescribing information).

Patients With Hepatic Impairment

Rezulin should be used with caution in patients with hepatic disease (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism in package insert for full prescribing information).

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