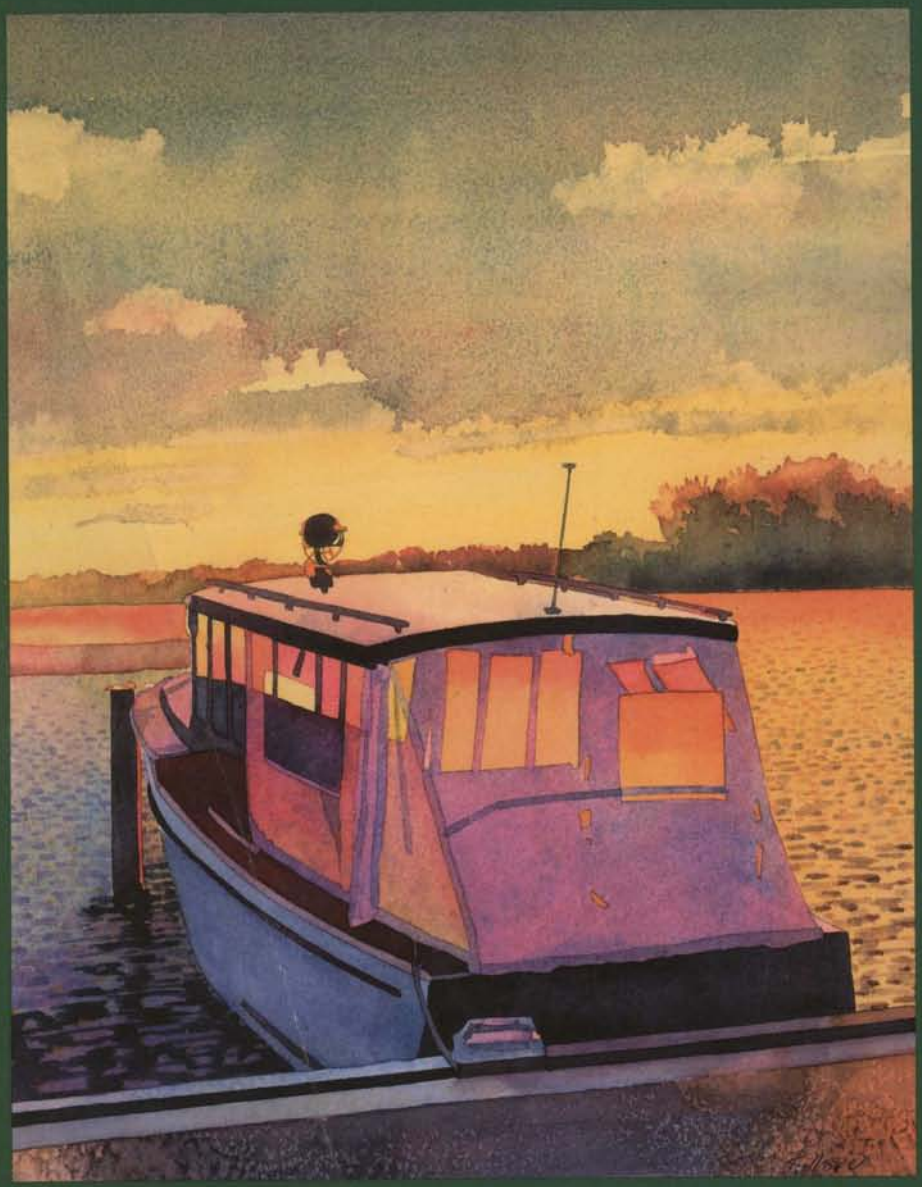
THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

VOLUME 21 NUMBER 3

Diabetes Care

MARCH 1998 WWW.DIABETES.ORG/DIABETESCARE



Well-being, cerebral function, and physical fatigue after nocturnal hypoglycemia in IDDM
P. King, M.-F. Kong, H. Parkin, I.A. Macdonald, R.B. Tattersall

High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men: 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study
B. Balkau, M. Shipley, R.J. Jarrett, K. Pyörälä, M. Pyörälä, A. Forhan, E. Eschwège

Neuropsychological complications of IDDM in children 2 years after disease onset
E.A. Northam, P.J. Anderson, G.A. Werther, G.L. Warne, R.G. Adler, D. Andrewes

Advances toward the implantable artificial pancreas for treatment of diabetes
J. Jaremko, O. Rorstad

Table of Contents on page v

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.**

Choose it for improved patient **quality of life.**[1]

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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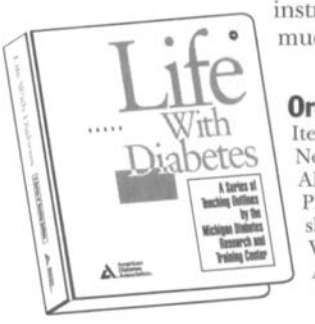

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THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

VOLUME 21 NUMBER 3

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. To achieve these goals, the journal publishes original articles on human studies in the following four categories: *1)* clinical care/education/nutrition, 2) epidemiology/health services/psychosocial research, 3) emerging treatments and technologies, and 4) pathophysiology/complications. The journal also publishes clinically relevant review articles, letters to the editor, and health/medical news or points of view. Topics covered are of interest to clinically oriented physicians, researchers, epidemiologists, psychologists, diabetes educators, and other health professionals.

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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.

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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.

American Diabetes Association.
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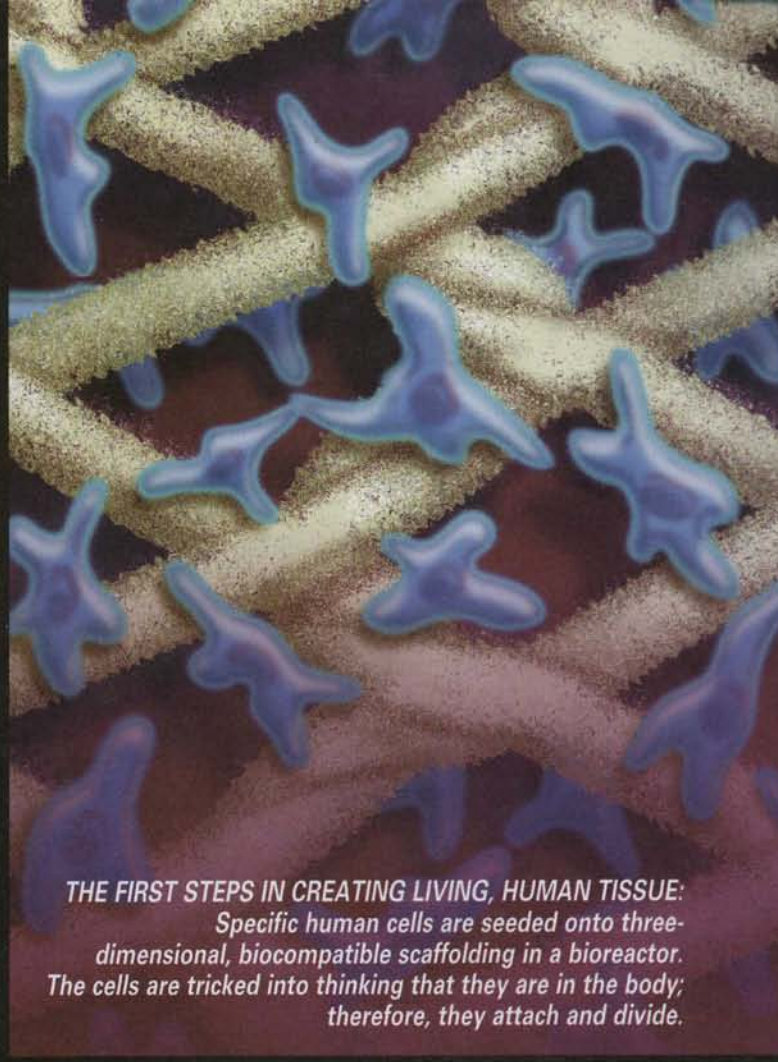
Tissue engineering from Advanced Tissue Sciences, Inc., and Smith & Nephew . . .

BRINGING NEW LIFE TO THE SCIENCE OF TISSUE REPAIR.



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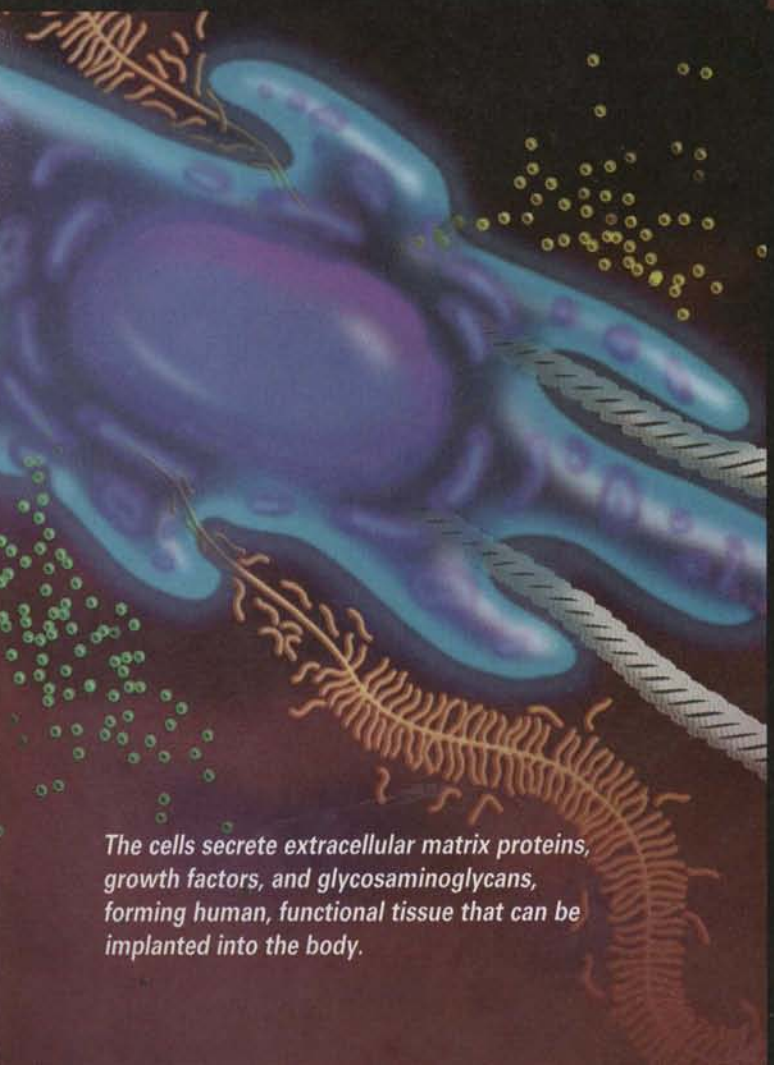

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MARCH 1998 VOLUME 21 NUMBER 3

Diabetes Care

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

Editorials

Original Articles

Clinical Care/Education/Nutrition

Epidemiology/Health Services/Psychosocial Research

Emerging Treatments and Technologies

Pathophysiology/Complications

Reviews/Commentaries/Position Statements

Table of Contents continues on page vi

Letters

MARCH AUTHOR INDEX
(VOLUME 21, NUMBER 3)

COVER: *Weekend Getaways on the Patuxent River* by Bobbi Tull, 1987. Watercolor, 10" × 12".

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INSULIN-SPARING GLUCOSE CONTROL

ONCE-A-DAY

Amaryl®

glimepiride TABLETS

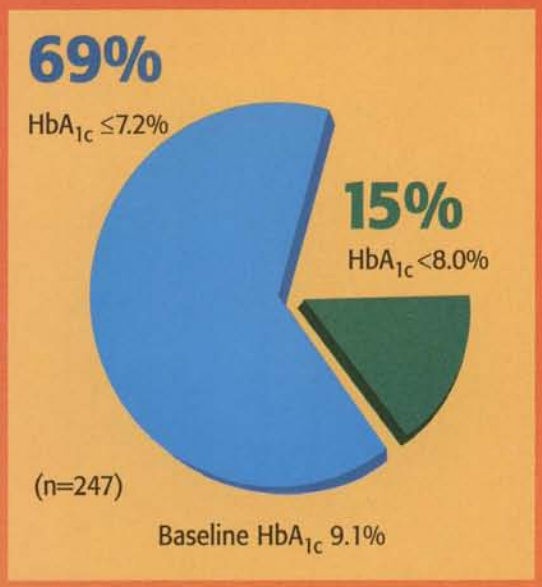
Please see brief summary of prescribing information on back.

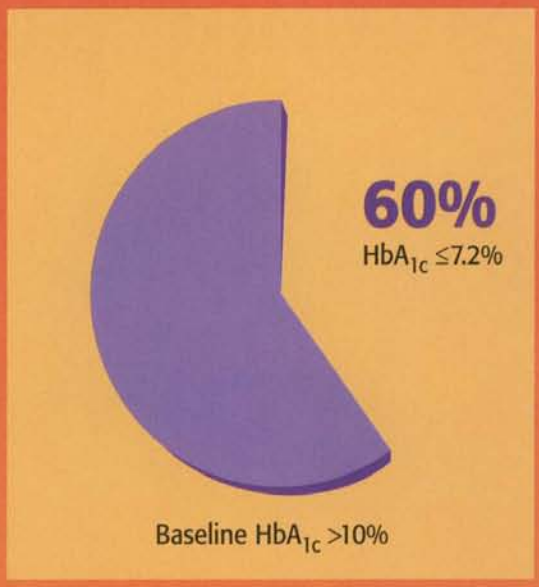
FEATURES LATEST CLINICAL RESULTS

A first-line, first-choice sulfonylurea

AMARYL DELIVERS HIGHLY EFFECTIVE GLUCOSE CONTROL[1,2*]

HbA_{1c} ≤7.2% is defined as tight control by the DCCT[3]



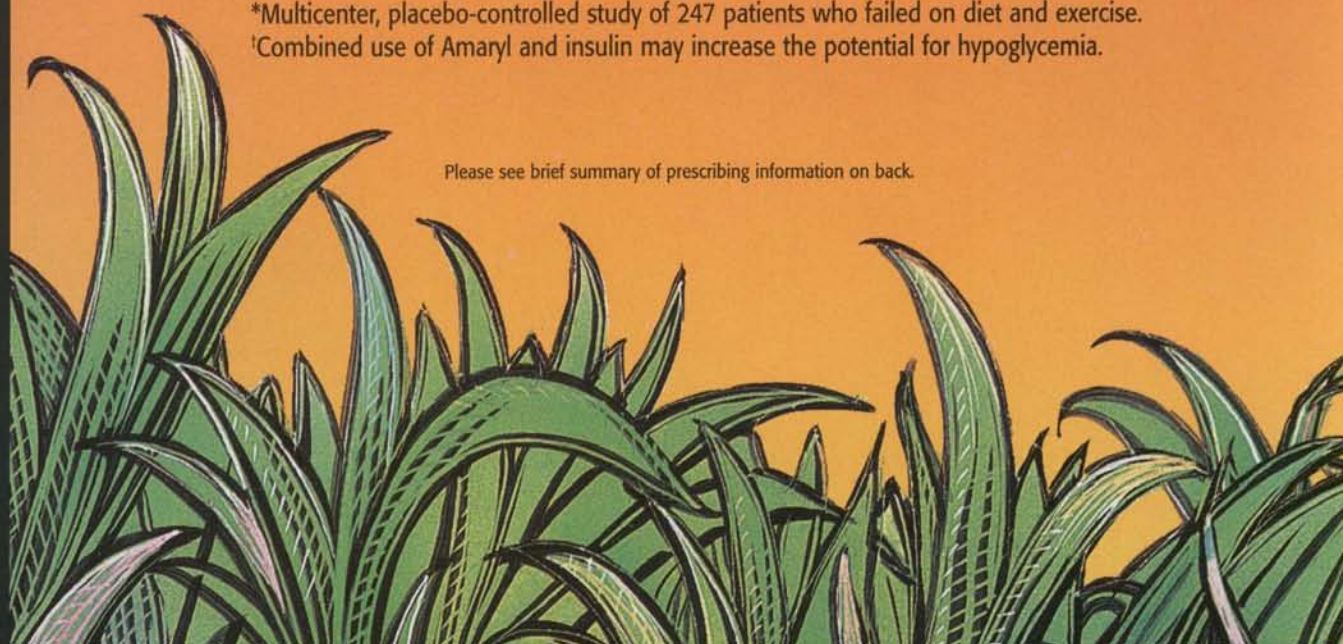


FAVORABLE SAFETY PROFILE

- 0.9% to 1.7% incidence of hypoglycemia as documented by blood glucose <60 mg/dL[2]
- Most common adverse reactions (>1%) include dizziness (1.7%), asthenia (1.6%), headache (1.5%), and nausea (1.1%)
- 60% renal, 40% hepatic dual route of elimination—100% biotransformed

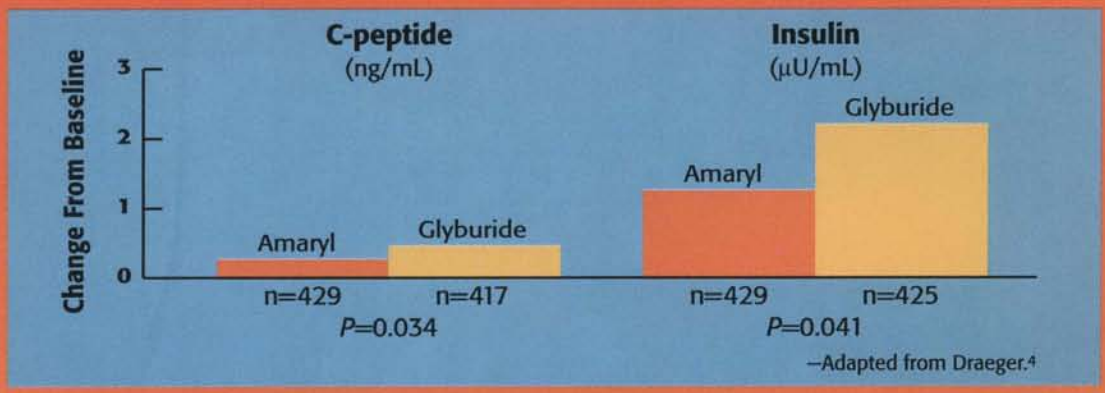
*Multicenter, placebo-controlled study of 247 patients who failed on diet and exercise.
†Combined use of Amaryl and insulin may increase the potential for hypoglycemia.

Please see brief summary of prescribing information on back.



CLINICAL STUDIES DEMONSTRATE INSULIN-SPARING GLUCOSE CONTROL

- One year of Amaryl treatment led to a smaller increase from baseline of fasting insulin and C-peptide levels than did 1 year of glyburide with comparable blood glucose control (n=1044)[4]



—Adapted from Draeger.[4]

PROVEN 24-HOUR CONTROL WITH ONCE-DAILY DOSING

- Indicated as an adjunct to diet and exercise for both monotherapy and in combination with insulin during second-line therapy[1]

ONCE-A-DAY

Amaryl®

glimepiride TABLETS

Insulin-sparing glucose control

Brief Summary of
Prescribing Information as of November 1996

Amaryl®
glimepiride* TABLETS

1, 2, and 4 mg

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

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

Coadministration of aspirin (1 g tid) and AMARYL® led to a 34% decrease in the mean glimepiride AUC and, therefore, a 34% increase in the mean CL/f. The mean C_{max} had a decrease of 4%. Blood glucose and serum C-peptide concentrations were unaffected and no hypoglycemic symptoms were reported. Pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of aspirin and other salicylates.

Coadministration of either cimetidine (800 mg once daily) or ranitidine (150 mg bid) with a single 4-mg oral dose of AMARYL® did not significantly alter the absorption and disposition of glimepiride, and no differences were seen in hypoglycemic symptomatology. Pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of H2-receptor antagonists.

Concomitant administration of propranolol (40 mg tid) and AMARYL® significantly increased C_{max}, AUC, and $T_{1/2}$ of glimepiride by 23%, 22%, and 15%, respectively, and it decreased CL/f by 18%. The recovery of M1 and M2 from urine, however, did not change. The pharmacodynamic responses to glimepiride were nearly identical in normal subjects receiving propranolol and placebo. Pooled data from clinical trials in patients with NIDDM showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of beta-blockers. However, if beta-blockers are used, caution should be exercised and patients should be warned about the potential for hypoglycemia.

Concomitant administration of AMARYL® (glimepiride tablets) (4 mg once daily) did not alter the pharmacokinetic characteristics of R- and S-warfarin enantiomers following administration of a single dose (25 mg) of racemic warfarin to healthy subjects. No changes were observed in warfarin plasma protein binding. AMARYL® treatment did result in a slight, but statistically significant, decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and maximum PT values during AMARYL® treatment were very small (3.3% and 9.9%, respectively) and are unlikely to be clinically important.

The responses of serum glucose, insulin, C-peptide, and plasma glucagon to 2 mg AMARYL® were unaffected by coadministration of ramipril (an ACE inhibitor) 5 mg once daily in normal subjects. No hypoglycemic symptoms were reported. Pooled data from clinical trials in patients with NIDDM showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of ACE inhibitors.

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. Potential interactions of glimepiride with other drugs metabolized by cytochrome P450 II C9 also include phenytoin, diclofenac, ibuprofen, naproxen, and mefenamic acid.

Although no specific interaction studies were performed, pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of calcium-channel blockers, estrogens, fibrates, NSAIDS, HMG CoA reductase inhibitors, sulfonamides, or thyroid hormone.

INDICATIONS AND USAGE

AMARYL® is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with noninsulin-dependent (Type II) diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet and exercise alone.

AMARYL® is also indicated for use in combination with insulin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic agent. Combined use of glimepiride and insulin may increase the potential for hypoglycemia.

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

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

During maintenance programs, AMARYL® monotherapy should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations. Secondary failures to AMARYL® monotherapy can be treated with AMARYL®-insulin combination therapy.

In considering the use of AMARYL® in asymptomatic patients, it should be recognized that blood glucose control in NIDDM has not definitely been established to be effective in preventing the long-term cardiovascular and neural complications of diabetes. However, the Diabetes Control and Complications Trial (DCCT) demonstrated that control of HbA1c and glucose was associated with a decrease in retinopathy, neuropathy, and nephropathy for insulin-dependent diabetic (IDDM) patients.

CONTRAINDICATIONS

AMARYL® is contraindicated in patients with

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

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

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

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

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

PRECAUTIONS

General

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Patients with impaired renal function may be more sensitive to the glucose-lowering effect of AMARYL®. A starting dose of 1 mg once daily followed by appropriate dose titration is recommended in those patients. Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. 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 add insulin in combination with AMARYL® or even use insulin monotherapy. The effectiveness of any oral hypoglycemic drug, including AMARYL®, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given. Should secondary failure occur with AMARYL® monotherapy, AMARYL®-insulin combination therapy may be instituted. Combined use of glimepiride and insulin may increase the potential for hypoglycemia.

Information for Patients

Patients should be informed of the potential risks and advantages of AMARYL® and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. The potential for primary and secondary failure should also be explained.

Laboratory Tests

Fasting blood glucose should be monitored periodically to determine therapeutic response. Glycosylated hemoglobin should also be monitored, usually every 3 to 6 months, to more precisely assess long-term glycemic control.

Drug Interactions

(See **CLINICAL PHARMACOLOGY, Drug Interactions.**)

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies in rats at doses of up to 5000 ppm in complete feed (approximately 340 times the maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation which was dose related and is thought to be the result of chronic pancreatic stimulation. The no-effect dose for adenoma formation in mice in this study was 320 ppm in complete feed, or 46-54 mg/kg body weight/day. This is about 35 times the maximum human recommended dose of 8 mg once daily based on surface area.

Glimepiride was non-mutagenic in a battery of *in vitro* and *in vivo* mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, mouse micronucleus test).

There was no effect of glimepiride on male mouse fertility in animals exposed up to 2500 mg/kg body weight (>1,700 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area).

Pregnancy

Teratogenic Effects. Pregnancy Category C. Glimepiride did not produce teratogenic effects in rats exposed orally up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately 60 times the maximum recommended human dose based on surface area). Glimepiride has been shown to be associated with intrauterine fetal death in rats when given in doses as low as 50 times the human dose based on surface area and in rabbits when given in doses as low as 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses inducing maternal hypoglycemia, has been similarly noted with other sulfonylureas, and is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride.

There are no adequate and well-controlled studies in pregnant women. On the basis of results from animal studies, AMARYL® (glimepiride tablets) should not be used during pregnancy. Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain glucose levels as close to normal as possible.

Nonteratogenic Effects. In some studies in rats, offspring of dams exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. Significant concentrations of glimepiride were observed in the serum and breast milk of the dams as well as in the serum of the pups. These skeletal deformations were determined to be the result of nursing from mothers exposed to glimepiride.

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. Patients who are planning a pregnancy should consult their physician, and it is recommended that they change over to insulin for the entire course of pregnancy and lactation.

Nursing Mothers

In rat reproduction studies, significant concentrations of glimepiride were observed in the serum and breast milk of the dams, as well as in the serum of the pups. Although it is not known whether AMARYL® is excreted in human milk, other sulfonylureas are excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, and because of the effects on nursing animals, AMARYL® should be discontinued in nursing mothers. If AMARYL® is discontinued, and if diet and exercise alone are inadequate for controlling blood glucose, insulin therapy should be considered. (See above ***Pregnancy*, Nonteratogenic Effects.**)

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The incidence of hypoglycemia with AMARYL®, as documented by blood glucose values < 60 mg/dL, ranged from 0.9-1.7% in two large, well-controlled, 1-year studies. (See **WARNINGS** and **PRECAUTIONS.**)

AMARYL® has been evaluated for safety in 2,013 patients in US controlled trials, and in 1,551 patients in foreign controlled trials. More than 1,650 of these patients were treated for at least 1 year.

Adverse events, other than hypoglycemia, considered to be possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with AMARYL® are shown below.

Adverse Events Occurring in ≥ 1% AMARYL® Patients

	AMARYL®		Placebo	
	No.	%	No.	%
Total Treated	746	100	294	100
Dizziness	13	1.7	1	0.3
Asthenia	12	1.6	3	1.0
Headache	11	1.5	4	1.4
Nausea	8	1.1	0	0.0

Gastrointestinal Reactions

Vomiting, gastrointestinal pain, and diarrhea have been reported, but the incidence in placebo-controlled trials was less than 1%. Isolated transaminase elevations have been reported. Cholestatic jaundice has been reported to occur rarely with sulfonylureas.

Dermatologic Reactions

Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients. These may be transient and may disappear despite continued use of AMARYL®; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Hematologic Reactions

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

Metabolic Reactions

Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas; however, no cases have yet been reported with AMARYL® (glimepiride tablets). Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

Other Reactions

Changes in accommodation and/or blurred vision may occur with the use of AMARYL®. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated. This condition is also seen in untreated diabetic patients, and may actually be reduced by treatment. In placebo-controlled trials of AMARYL®, the incidence of blurred vision was placebo, 0.7%, and AMARYL®, 0.4%.

Prescribing Information as of November 1996

Hoechst-Roussel Pharmaceuticals
Division of Hoechst Marion Roussel, Inc.
Kansas City, MO 64137 USA

US Patent 4,379,785

amab1196b

References: 1. Schade DS, Jovanovic-Peterson L, Schneider J. A placebo-controlled, randomized study of glimepiride in patients with non-insulin-dependent diabetes mellitus (NIDDM): sustained glucose control with minimal fasting plasma insulin changes. Submitted for publication. **2.** Data on file, Hoechst Marion Roussel. **3.** American Diabetes Association. Position statement: implications of the Diabetes Control and Complications Trial. *Diabetes.* 1993;42:1555-1558. **4.** Draeger KE, Wernicke-Panten K, Lomp H-J, Schüler E, Roβkamp R. Long-term treatment of type 2 diabetic patients with the new oral antidiabetic agent glimepiride (Amaryl®): a double-blind comparison with glibenclamide. *Horm Metab Res.* 1996;28:419-425.

97316101/2707R7

Hoechst Marion Roussel

The Pharmaceutical Company of Hoechst
Kansas City, MO 64134

Hoechst

Help protect patients at risk of First MI

In asymptomatic patients age 45 and older...hypercholesterolemic...
with one or more additional cardiovascular risk factors

Pravachol is proven to reduce the risk of First MI by 31%*[1]

First MI First MI First MI

Pravachol is well tolerated. The most common adverse events are rash, fatigue, headache, and dizziness. Pravachol is contraindicated in the presence of active liver disease or unexplained persistent transaminase elevations, or for patients who are pregnant or nursing. • It is recommended that liver function tests be performed prior to and at 12 weeks following initiation of therapy or an elevation in dose. If a patient develops increased transaminase levels, or signs and symptoms of liver disease, more frequent monitoring may be required. • Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Discontinue pravastatin if myopathy is diagnosed or suspected. • The combined use of pravastatin and fibrates should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

In addition to diet, when diet and other nonpharmacological measures have been inadequate, in hypercholesterolemic patients without clinically evident coronary heart disease, Pravachol is indicated to reduce the risk of myocardial infarction; reduce the risk of undergoing myocardial revascularization procedures; reduce the risk of cardiovascular mortality with no increase in death from noncardiovascular causes.

It is not clear to what extent the findings of this study can be extrapolated to a similar population of women.

Please see CONTRAINDICATIONS, WARNINGS (including Skeletal Muscle), PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information adjacent to this advertisement.

*$p = 0.0001$

Reference: 1. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med.* 1995; 333:1301-1307.

PRAVACHOL®
pravastatin sodium 20 mg tablets

Bristol-Myers Squibb Company

D3-K033C

Issued: March 1998

PRAVACHOL®

Pravastatin Sodium Tablets

CONTRAINDICATIONS: Hypersensitivity to any component of this medication. Active liver disease or unexplained, persistent elevations in liver function tests (see **WARNINGS**). *Pregnancy and lactation.* Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease *cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may* cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS: Liver Enzymes: *HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated* with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the US over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients. In the largest long-term placebo-controlled clinical trial with pravastatin (Pravastatin Primary Prevention Study; See **Clinical Pharmacology**), the overall incidence of AST and/or ALT elevations to greater than three times the upper limit of normal was 1.05% in the pravastatin group as compared to 0.75% in the placebo group. One (0.03%) pravastatin-treated patient and 2 (0.06%) placebo-treated patients were discontinued because of transaminase elevations. Of the patients with normal liver function at week 12, three of 2875 treated with pravastatin (0.10%) and one of the 2919 placebo patients (0.03%) had elevations of AST greater than three times the upper limit of normal on two consecutive measurements and/or discontinued due to elevations in transaminase levels during the 4.8 years (median treatment) of the study. **It is recommended that liver function tests be performed prior to and at 12 weeks following initiation of therapy or the elevation of dose.** Patients who develop increased transaminase levels or signs and symptoms of liver disease should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of pravastatin therapy is recommended. Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see **CONTRAINDICATIONS**). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see **CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism**). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect. **Skeletal Muscle: Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with pravastatin and other drugs in this class.** Uncomplicated myalgia has also been reported in pravastatin-treated patients (see **ADVERSE REACTIONS**). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper normal limit, was rare (< 0.1%) in pravastatin clinical trials. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.** The risk of myopathy during treatment with another HMG-CoA reductase inhibitor is increased with concurrent therapy with either erythromycin, cyclosporine, niacin, or fibrates. However, neither myopathy nor significant increases in CPK levels have been observed in three reports involving a total of 100 post-transplant patients (24 renal and 76 cardiac) treated for up to two years concurrently with pravastatin 10-40 mg and cyclosporine. Some of these patients also received other concomitant immunosuppressive therapies. In one single-dose study, pravastatin levels were found to be increased in cardiac transplant patients receiving cyclosporine. Further, in clinical trials involving small numbers of patients who were treated concurrently with pravastatin and niacin, there were no reports of myopathy. Also, myopathy was not reported in a trial of combination pravastatin (40 mg/day) and gemfibrozil (1200 mg/day), although 4 of 75 patients on the combination showed marked CPK elevations versus one of 73 patients receiving placebo. There was a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy (see **PRECAUTIONS: Drug Interactions**). **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.**

PRECAUTIONS: General: Pravastatin may elevate creatinine phosphokinase and transaminase levels (see **ADVERSE REACTIONS**). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin. *Homozygous Familial Hypercholesterolemia.* Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors. *Renal Insufficiency.* A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life ($t_{1/2}$) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored. **Information for Patients:** Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Drug Interactions:** *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See **WARNINGS: Skeletal Muscle**. *Antipyrine:* Since concomitant administration of pravastatin had no effect on the clearance of antipyrine, interactions with other drugs metabolized via the same hepatic cytochrome isozymes are not expected. *Cholestyramine/Colestipol:* Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See **DOSAGE AND ADMINISTRATION: Concomitant Therapy**.) *Warfarin:* In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed. *Cimetidine:* The $AUC_{0\text{-}12\ hr}$ for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid. *Digoxin:* In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered. *Cyclosporine:* Some investigators have measured cyclosporine levels in patients on pravastatin, and to date, these results indicate no clinically meaningful elevations in cyclosporine levels. In one single-dose study, pravastatin levels were found to be increased in cardiac transplant patients receiving cyclosporine. *Gemfibrozil:* In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and Tmax for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended. In interaction studies with *aspirin, antacids* (1 hour prior to PRAVACHOL), *cimetidine, nicotinic acid,* or *probucol*, no statistically significant differences in bioavailability were seen when PRAVACHOL (pravastatin sodium) was administered. *Other Drugs:* During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, ACE inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin. **Endocrine Function:** HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p < 0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥ 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones. **CNS Toxicity:** CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans *taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced* vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p < 0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC. The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times the human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p < 0.05$). The incidence was not dose-related and male mice were not affected. A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/- mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice. In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). *In rats treated with this same* reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear. **Pregnancy: Pregnancy Category X.** See **CONTRAINDICATIONS**. Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area ($mg/meter^2$). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (Vater association) in a baby born to a woman who took another HMG-CoA reductase inhibitor with dextroamphetamine sulfate during the first trimester of pregnancy. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL (pravastatin sodium), it should be discontinued *and the patient advised again as to the potential hazards to the fetus.* **Nursing Mothers:** *A small amount of pravastatin* is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see **CONTRAINDICATIONS**). **Pediatric Use:** Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time.

ADVERSE REACTIONS: Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. *In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were* discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients. **Adverse Clinical Events:** All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

	All Events		Events Attributed to Study Drug	
Body System/Event	**Pravastatin (N = 900) %**	**Placebo (N = 411) %**	**Pravastatin (N = 900) %**	**Placebo (N = 411) %**
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

In the Pravastatin Primary Prevention Study (West of Scotland Coronary Prevention Study) (see **CLINICAL PHARMACOLOGY: Clinical Studies**) involving 6595 patients treated with PRAVACHOL (pravastatin sodium) (N = 3302) or placebo (n = 3293) the adverse event profile in the pravastatin group was comparable to that of the placebo group over the median 4.8 years of the study. The following effects have been reported with drugs in this class; not all the effects listed below have necessarily been associated with pravastatin therapy: *Skeletal:* myopathy, rhabdomyolysis, arthralgia. *Neurological:* dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression. *Hypersensitivity Reactions:* An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, *eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal* necrolysis, erythema multiforme, including Stevens-Johnson syndrome. *Gastrointestinal:* pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting. *Skin:* alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported. *Reproductive:* gynecomastia, loss of libido, erectile dysfunction. *Eye:* progression of cataracts (lens opacities), ophthalmoplegia. *Laboratory Abnormalities:* elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities. **Laboratory Test Abnormalities:** Increases in serum transaminase (ALT, AST) values and CPK have been observed (see **WARNINGS**). Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with HMG-CoA reductase inhibitors. **Concomitant Therapy:** Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See **WARNINGS: Skeletal Muscle** and **PRECAUTIONS: Drug Interactions**.)

OVERDOSAGE: To date, there are two reported cases of overdosage with pravastatin, both of which were asymptomatic and not associated with clinical laboratory abnormalities. If an overdose occurs, it should be treated symptomatically and supportive measures should be instituted as required.

CAUTION: Federal (USA) law prohibits dispensing without prescription.

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Revised April 1997
D3-B001-4-97

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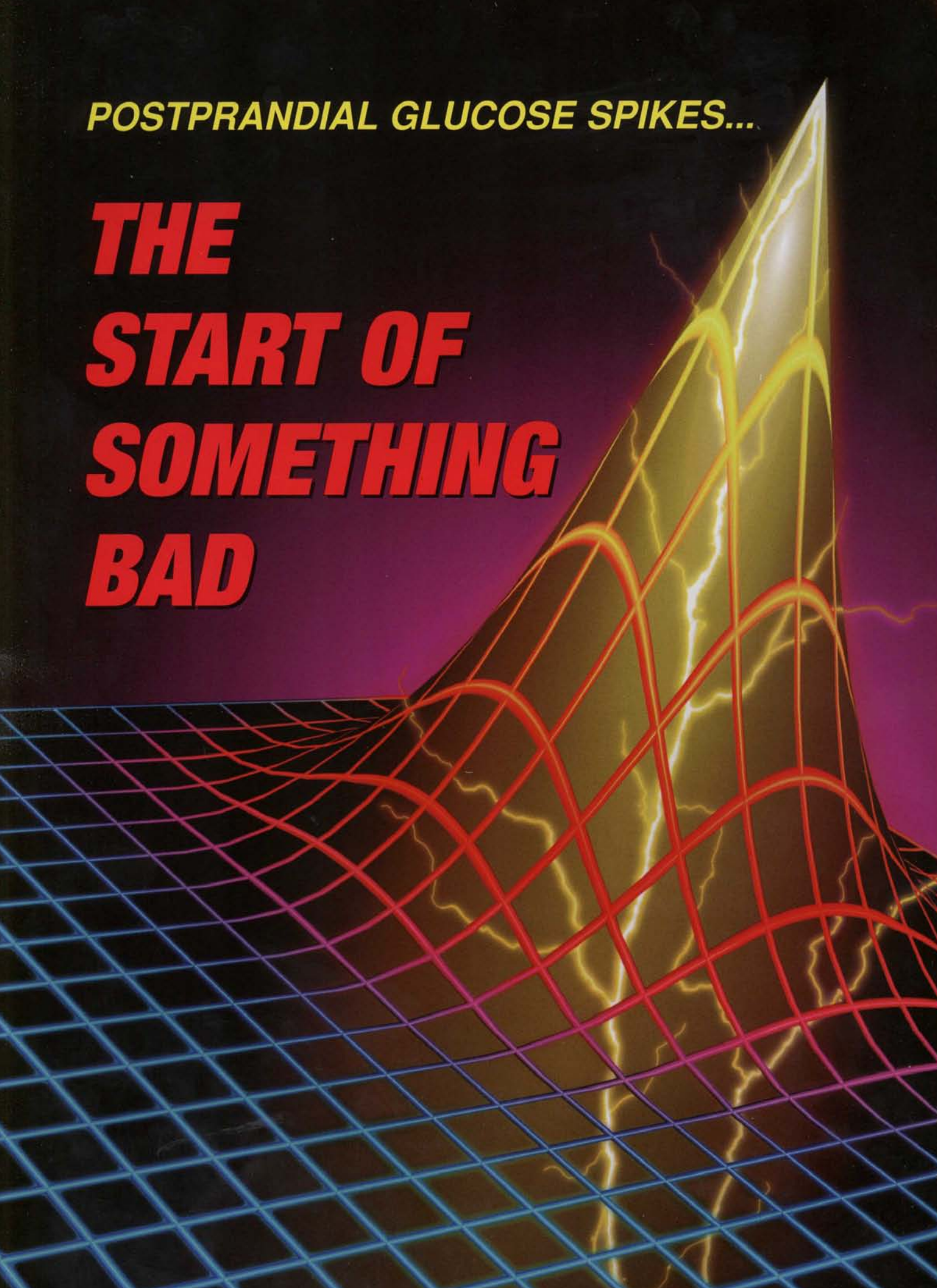
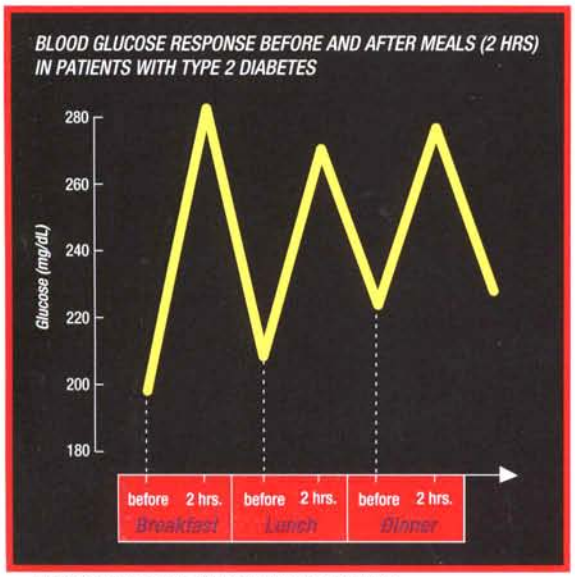

POSTPRANDIAL GLUCOSE SPIKES...
THE START OF SOMETHING BAD

Uncontrolled Postprandial Glucose (PPG) Spikes: A Danger in Type 2 Diabetes

Every PPG Spike Contributes to the Risk of Diabetic Complications

- *PPG spikes have been linked to[1-6]:*
  - *— nephropathy*
  - *— retinopathy*
  - *— neuropathy*
  - *— atherosclerosis*
  - *— myocardial infarction*



Artist representation of blood glucose over time.

- *Even well-controlled type 2 diabetes patients have elevated postprandial hyperglycemia[7]*
- *PPG spikes may predispose cells or tissues to damage from hyperglycemia[1]*
- *Daily PPG spikes can raise HbA1c by more than 0.5%[1]*

TREATMENT OF PPG IS CRITICAL TO ACHIEVE OPTIMAL CLINICAL OUTCOMES IN TYPE 2 DIABETES[8]

References: 1. Santiago JV. Glucose control in diabetes mellitus: role of acarbose in reducing postprandial hyperglycemia. *Drug Benefit Trends.* 1996;8(suppl):27-35. 2. American Diabetes Association. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care.* 1997;20(7):1183-1197. 3. Pettitt DJ, Knowler WC, Lisse JR, Bennett PH. Development of retinopathy and proteinuria in relation to plasma-glucose concentrations in Pima Indians. *Lancet.* 1980:1050-1052. 4. Portha B, Ktorza A. Glucotoxicite et secretion d'insuline. *Diabetologie.* 1996:121-131. 5. Yamasaki Y, Kawamori R, Matsushima H, et al. Asymptomatic hyperglycaemia is associated with increased intimal plus medial thickness of the carotid artery. *Diabetologia.* 1995;38:585-591. 6. Hanefeld M, Fischer S, Julius U, et al. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia.* 1996;39(12):1577-1583. 7. Keen H. Glucomodulation: a new therapeutic approach. *Practical Diabetes Supplement.* 1993;10(6):S5-S9. 8. American Diabetes Association. Implications of the Diabetes Control and Complications Trial. *Diabetes Care.*1993;16(11):1517-1520.

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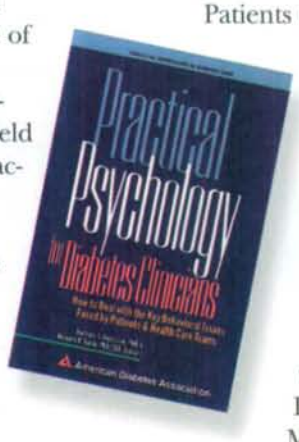

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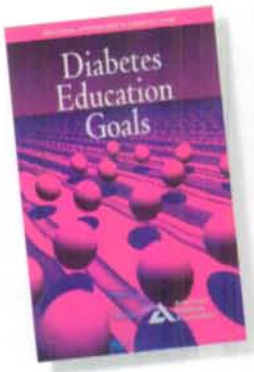

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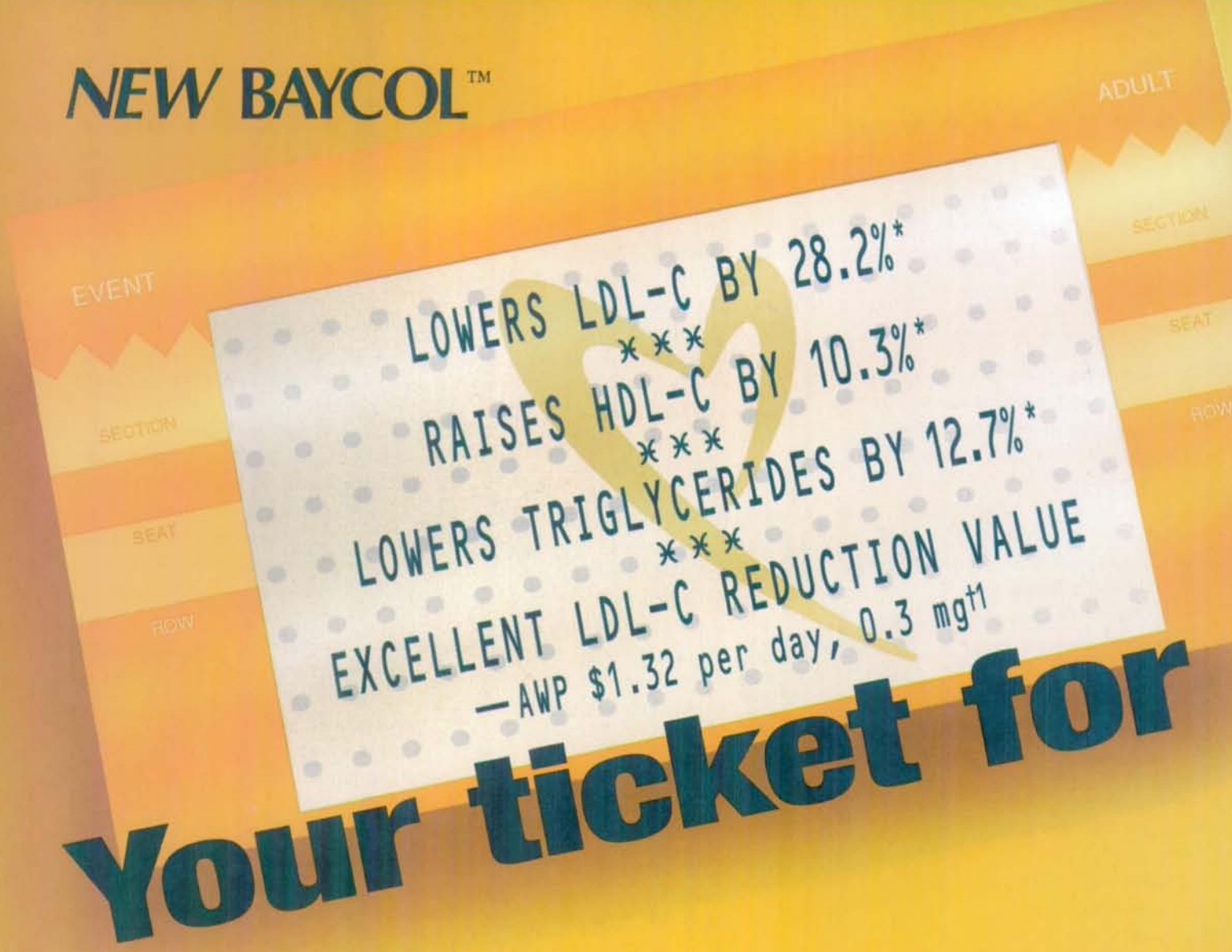

Baycol™ (cerivastatin sodium tablets) is indicated as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Types IIa and IIb) when the response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures alone have been inadequate.

The effect of *Baycol* on cardiovascular morbidity and mortality has not been determined.

Important Safety Information

Baycol is contraindicated in patients with hypersensitivity to any component of this medication, in patients with active liver disease or unexplained persistent elevations of serum transaminases, in women during pregnancy and in nursing mothers.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of plasma creatine kinase (CK). Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. *Baycol* therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected.

It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter, e.g., semiannually.

In clinical trials with over 3,000 patients, the most common adverse events regardless of causality were rhinitis, pharyngitis, headache, dyspepsia, diarrhea, arthralgia and myalgia.

*Results reflect mean percent change from baseline, in a 24-week, randomized, double-blind, placebo-controlled U.S. trial in 934 patients with primary hypercholesterolemia. Reductions may vary from patient to patient.

performance and value

[1]Average wholesale price (AWP) based on per day cost of 0.3 mg tablets, bottles of 100. AWP is from a published price list and may or may not represent actual price to pharmacists or consumers. Retail pricing may vary from community to community and may affect cost savings for the patient.

Reference: 1. *Red Book® Update.* January 1998. In press.

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Please see brief summary of prescribing information on next page.

BAYCOL™
(cerivastatin sodium tablets)

BRIEF SUMMARY
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PZ500041BS 7/97

INDICATIONS AND USAGE: Therapy with lipid-altering drugs should be a component of multiple risk factor intervention in those patients at significantly high risk for atherosclerotic vascular disease due to hypercholesterolemia. BAYCOL™ (cerivastatin sodium tablets) is indicated as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients *with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Types IIa and IIb) when the response to dietary* restriction of saturated fat and cholesterol and other non-pharmacological measures alone has been inadequate.

Before considering therapy with lipid-altering agents, secondary causes of hypercholesterolemia, e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism, should be excluded and a lipid profile performed to measure Total-C, HDL-C, and triglycerides (TG). For patients with TG less than 400 mg/dL, LDL-C can be estimated using the following equation: LDL-C = [Total-C] minus [HDL-C + TG/5]

For TG levels > 400 mg/dL, this equation is less accurate and LDL-C concentrations should be directly measured by preparative ultracentrifugation. In many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated Total-C. In such cases, BAYCOL™ (cerivastatin sodium tablets) is not indicated.

Lipid determinations should be performed at intervals of no less than four weeks.

The National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized in Table 2.

Table 2 National Cholesterol Education Program (NCEP) Treatment Guidelines

	LDL-Cholesterol mg/dL (mmol/L)		
Definite Atherosclerotic Disease*	**Two or More Other Risk Factors****	**Initiation Level*****	**Goal**
NO	NO	≥ 190 (≥ 4.9)	< 160 (<4.1)
NO	YES	≥ 160 (≥ 4.1)	< 130 (<3.4)
YES	YES or NO	≥ 130 (≥ 3.4)	< 100 (<2.6)

* Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

** Other risk factors for coronary heart disease (CHD) include the following: age (males: ≥ 45 years; females: ≥ 55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C < 35 mg/dL (< 0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is ≥ 60 mg/dL (≥ 1.6 mmol/L).

*** In CHD patients with LDL-C levels 100-129 mg/dL, the physician should exercise clinical judgement in deciding whether to initiate drug treatment.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C level is ≥ 130 mg/dL (NCEP-ATP II).

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the Total-C be used to monitor therapy.

Although BAYCOL™may be useful to reduce elevated LDL-cholesterol levels in patients with combined hypercholesterolemia and hypertriglyceridemia where hypercholesterolemia is the major abnormality (Type IIb hyperlipoproteinemia), it has not been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL, or IDL (i.e., hyperlipoproteinemia types I, III, IV, or V).[1]

CONTRAINDICATIONS: Active liver disease or unexplained persistent elevations of serum transaminases (see **WARNINGS**).

Pregnancy and lactation: Atherosclerosis is a chronic process, and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Cerivastatin sodium should be administered to women of child-bearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this drug, cerivastatin sodium should be discontinued and the patient should be apprised of the potential hazard to the fetus.

Hypersensitivity to any component of this medication.

WARNINGS: ***Liver Enzymes:*** HMG-CoA reductase inhibitors have been associated with biochemical abnormalities of liver function. Persistent increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal (occurring on two or more not necessarily sequential occasions) have been reported in less than 1.0% of patients treated with cerivastatin sodium in the US over an average period of 11 months. Most of these abnormalities occurred within the first 6 weeks of treatment, resolved after discontinuation of the drug, and were not associated with cholestasis. In most cases, these biochemical abnormalities were asymptomatic.

It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter, e.g., semiannually. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of cerivastatin sodium therapy is recommended.

Active liver disease or unexplained transaminase elevations are contraindications to the use of BAYCOL™ (cerivastatin sodium tablets) (see **CONTRAINDICATIONS**). Caution should be exercised when cerivastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion (see **CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism**). Such patients should be started at the low end of the recommended dosing range and closely monitored.

Skeletal Muscle: **Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with other HMG-CoA reductase inhibitors.** Myopathy, defined as muscle aching or muscle weakness, associated with increases in plasma creatine kinase (CK) values to greater than 10 times the upper limit of normal, was rare (<0.2%) in U.S. cerivastatin clinical trials. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. BAYCOL™ (cerivastatin sodium tablets) therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected. **BAYCOL™ (cerivastatin sodium tablets) should be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with other HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, azole antifungals or lipid-lowering doses of niacin.

Uncomplicated myalgia has been observed infrequently in patients treated with cerivastatin sodium at rates that could not be distinguished from placebo.

The use of fibrates alone occasionally may be associated with myopathy. The combined use of HMG-CoA inhibitors and fibrates generally should be avoided.

PRECAUTIONS: General: Before instituting therapy with BAYCOL™ (cerivastatin sodium tablets), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in obese patients, and treatment of underlying medical problems (see INDICATIONS AND USAGE).

Cerivastatin sodium may elevate creatine kinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with cerivastatin sodium.

Homozygous Familial Hypercholesterolemia: Cerivastatin sodium has not been evaluated in patients with rare homozygous familial hypercholesterolemia. HMG-CoA reductase inhibitors have been reported to be less effective in these patients because they lack functional LDL receptors.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Fibric Acid Derivatives, Niacin (Nicotinic Acid), Erythromycin, Azole Antifungals: See WARNINGS: Skeletal Muscle.

ANTACID (Magnesium-Aluminum Hydroxide): Cerivastatin plasma concentrations were not affected by co-administration of antacid.

CIMETIDINE: Cerivastatin plasma concentrations were not affected by co-administration of cimetidine.

CHOLESTYRAMINE: The influence of the bile-acid-sequestering agent cholestyramine on the pharmacokinetics of cerivastatin sodium was evaluated in 12 healthy males in 2 separate randomized crossover studies. In the first study, concomitant administration of 0.2 mg cerivastatin sodium and 12 g cholestyramine resulted in decreases of more than 22% for AUC and 40% for C_{max} when compared to dosing cerivastatin sodium alone. However, in the second study, administration of 12 g cholestyramine 1 hour before the evening meal and 0.3 mg cerivastatin sodium approximately 4 hours after the same evening meal resulted in a decrease in the cerivastatin AUC of less than 8%, and a decrease in C_{max} of about 30% when compared to dosing cerivastatin sodium alone. Therefore, it would be expected that a dosing schedule of cerivastatin sodium given at bedtime and cholestyramine given before the evening meal would not result in a significant decrease in the clinical effect of cerivastatin sodium.

DIGOXIN: Plasma digoxin levels and digoxin clearance at steady-state were not affected by co-administration of 0.2 mg cerivastatin sodium. Cerivastatin plasma concentrations were also not affected by co-administration of digoxin.

WARFARIN: Co-administration of warfarin and cerivastatin to healthy volunteers did not result in any changes in prothrombin time or clotting factor VII when compared to co-administration of warfarin and placebo. The AUC and C_{max} of both the (R) and (S) isomers of warfarin were unaffected by concurrent dosing of 0.3 mg cerivastatin sodium. Co-administration of warfarin and cerivastatin did not alter the pharmacokinetics of cerivastatin sodium.

ERYTHROMYCIN: In hypercholesterolemic patients, steady-state cerivastatin AUC and C_{max} increased approximately 50% and 24% respectively after 10 days with co-administration of erythromycin, a known inhibitor of cytochrome P450 3A4.

OTHER CONCOMITANT THERAPY: Although specific interaction studies were not performed, in clinical studies, cerivastatin sodium was used concomitantly with angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, calcium-channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production.

Clinical studies have shown that cerivastatin sodium has no adverse effect on sperm production and does not reduce basal plasma cortisol concentration, impair adrenal reserve or have an adverse effect on thyroid metabolism as assessed by TSH. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effect on basal and reserve steroid levels. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown.

Patients treated with cerivastatin sodium who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs that may decrease the levels or activity of endogenous steroid hormones, e.g., ketoconazole, spironolactone, or cimetidine.

CNS and other Toxicities: Chronic administration of cerivastatin to rodent and non-rodent species demonstrated the principal toxicologic targets and effects observed with other HMG-CoA reductase inhibitors: Hemorrhage and edema in multiple organs and tissues including CNS (dogs); cataracts (dogs); degeneration of muscle fibers (dogs, rats, and mice); hyperkeratosis in the nonglandular stomach (rats and mice, this organ has no human equivalent); liver lesions (dogs, rats, and mice).

CNS lesions were characterized by multifocal bleeding with fibrinoid degeneration of vessel walls in the plexus chorioideus of the brain stem and in the ciliary body of the eye at 0.1 mg/kg/day in the dog. This dose resulted in plasma levels of cerivastatin (C_{max}), that were about 23 times higher than the mean values in humans taking 0.3 mg/day. No CNS lesions were observed after chronic treatment with cerivastatin for up to two years in the mouse (C_{max} up to 7 times that of humans at 0.3 mg/day) and rat (C_{max} up to 2 times that of humans).

Carcinogenesis, Mutagenesis, Impairment of Fertility: A 2-year study was conducted in rats at average daily doses of cerivastatin of 0.007, 0.034, or 0.158 mg/kg. The high dosage level corresponded to plasma drug levels (AUC) of approximately 1 - 2 times the mean human plasma drug concentrations after a 0.3-mg oral dose. Tumor incidences of treated rats were comparable to controls in all treatment groups. In a 2-year carcinogenicity study in mice with average daily doses of cerivastatin of 0.4, 1.8, 9.1, or 55 mg/kg hepatocellular adenomas were significantly increased in male and female mice at ≥9.1 mg/kg and hepatocellular carcinomas were significantly increased in male mice at ≥1.8 mg/kg. These doses were in the range of human exposure (dose of 0.3 mg/day).

No evidence of genotoxicity was observed *in vitro* with or without metabolic activation in the following assays: microbial mutagen tests using mutant strains of *S. typhimurium* or *E. coli*, Chinese Hamster Ovary Forward Mutation Assay, Unscheduled DNA Synthesis in rat primary hepatocytes, chromosome aberrations in Chinese Hamster Ovary cells, and spindle inhibition in human lymphocytes. In addition, there was no evidence of genotoxicity *in vivo* in a mouse Micronucleus Test; there was equivocal evidence of mutagenicity in a mouse Dominant Lethal Test.

In a combined male and female rat fertility study, cerivastatin had no adverse effects on fertility or reproductive performance at doses up to 0.1 mg/kg/day, a dose that produced plasma drug levels (C_{max}) about 1 - 2 times higher than mean plasma drug levels for humans receiving 0.3 mg cerivastatin/day. At a dose of 0.3 mg/kg/day (plasma C_{max} 4 - 5 times the human level), the length of gestation was marginally prolonged, stillbirths were increased, and the survival rate up to day 4 postpartum was decreased. In the fetuses (F1), a marginal reduction in fetal weight and delay in bone development was observed. In the mating of the F1 generation, there was a reduced number of female rats that littered.

In the testicles of dogs treated chronically with cerivastatin at a dose of 0.008 mg/kg/day (approximately 2 fold the human exposure at doses of 0.3 mg based on C_{max}), atrophy, vacuolization of the germinal epithelium, spermatidic giant cells, and focal oligospermia were observed. In another 1-year study in dogs treated with 0.1 mg/kg/day (approximately 23 fold the human exposure at doses of 0.3 mg based on C_{max}), ejaculate volume was small and libido was decreased. Semen analysis revealed an increased number of morphologically altered spermatozoa indicating disturbances of epididymal sperm maturation that was reversible when drug administration was discontinued.

Pregnancy: Pregnancy Category X: (See CONTRAINDICATIONS): Cerivastatin caused a significant increase in incomplete ossification of the lumbar center of the vertebrae in rats at an oral dose of 0.72 mg/kg. Cerivastatin did not cause any anomalies or malformations in rabbits at oral doses up to 0.75 mg/kg. These doses resulted in plasma levels (C_{max}) 6-7 times the human exposure for rats and 3-4 times the human exposure for rabbits (human dose 0.3 mg). Cerivastatin crossed the placenta and was found in fetal liver, gastrointestinal tract, and kidneys when pregnant rats were given a single oral dose of 2 mg/kg.

Safety in pregnant women has not been established. Cerivastatin should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a three- to four-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with BAYCOL™ during pregnancy (see CONTRAINDICATIONS), treatment should be immediately discontinued as soon as pregnancy is recognized. If a women becomes pregnant while taking cerivastatin, the drug should be discontinued and the patient advised again as to potential hazards to the fetus.

Nursing Mothers: Based on preclinical data, cerivastatin is present in breast milk in a 1.3:1 ratio (milk:plasma). Because of the potential for serious adverse reactions in nursing infants, nursing women should not take cerivastatin (see CONTRAINDICATIONS).

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

Geriatric Use: *In clinical pharmacology studies, there were no clinically relevant effects of age on the pharmacokinetics of* cerivastatin sodium.

Renal Insufficiency: Patients with significant renal impairment ($Cl_{cr} \leq 60$ mL/min/1.73m^2) have increased AUC (up to 60%) and C_{max} (up to 23%) and should be administered BAYCOL™ with caution.

Hepatic Insufficiency: Safety and effectiveness in hepatically impaired patients have not been established. Cerivastatin should be used with caution in patients who have a history of liver disease and/or consume substantial quantities of alcohol (see Contraindications and Warnings).

ADVERSE REACTIONS: In the U.S. placebo-controlled clinical studies, discontinuations due to adverse events occurred in 3% of cerivastatin sodium treated patients and in 3% of patients treated with placebo. Adverse reactions have usually been mild and transient. Cerivastatin sodium has been evaluated for adverse events in more than 3,000 patients and is generally well-tolerated.

Clinical Adverse Experiences: Adverse experiences occurring with a frequency ≥2% for marketed doses of cerivastatin sodium, regardless of causality assessment, in U.S. placebo-controlled clinical studies, are shown in the Table 3 below:

Table 3 Adverse Experiences Occurring In ≥2% of Patients In U.S. Placebo-Controlled Clinical Studies

Adverse Event	BAYCOL™ (n = 552)	Placebo (n = 247)	Adverse Event	BAYCOL™ (n = 552)	Placebo (n = 247)
Body as a Whole			**Musculoskeletal**		
Headache	11.8%	12.6%	Arthralgia	6.7%	4.5%
Accidental Injury	7.1%	6.9%	Myalgia	2.7%	1.2%
Flu Syndrome	6.3%	8.1%	**Nervous**		
Back Pain	4.0%	6.1%	Dizziness	2.5%	3.6%
Abdominal Pain	3.4%	3.6%	Insomnia	2.2%	1.2%
Asthenia	3.4%	2.8%	**Respiratory**		
Chest Pain	2.9%	2.8%	Rhinitis	13.2%	12.1%
Leg Pain	2.0%	1.2%	Pharyngitis	12.0%	17.0%
Cardiovascular			Sinusitis	6.9%	5.7%
Peripheral Edema	2.0%	1.2%	Cough Increased	2.7%	2.0%
Digestive			**Skin and Appendages**		
Dyspepsia	5.6%	4.9%	Rash	3.4%	5.7%
Diarrhea	4.0%	3.6%	**Urogenital**		
Flatulence	3.4%	3.6%	Urinary Tract Infection	1.6%	2.4%
Nausea	2.7%	3.2%			
Constipation	1.8%	2.0%			
Surgery	1.4%	3.6%			

The following effects have been reported with drugs in this class.

Skeletal: myopathy, muscle cramps, rhabdomyolysis, arthralgias, myalgia.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, memory loss, vertigo, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression, psychic disturbances.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely that included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia, pruritus. A variety of skin changes, e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails, have been reported.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Concomitant Therapy: In studies where cerivastatin sodium has been administered concomitantly with cholestyramine, no adverse reactions unique to this combination or in addition to those previously reported for this class of drugs were reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, fibric acid derivatives, erythromycin, azole antifungals or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended (*See* WARNINGS: *Skeletal Muscle*).

References:

1 Classification of Hyperlipoproteinemias

		Lipid Elevations	
Type	Lipoproteins Elevated	major	minor
I (rare)	chylomicrons	TG	↑→C
IIa	LDL	C	–
IIb	LDL,VLDL	C	TG
III (rare)	IDL	C/TG	–
IV	VLDL	TG	↑→C
V (rare)	chylomicrons, VLDL	TG	↑→C

C=cholesterol, TG=triglycerides, LDL=low-density lipoprotein,
VLDL= very-low-density lipoprotein, IDL=intermediate-density lipoprotein.

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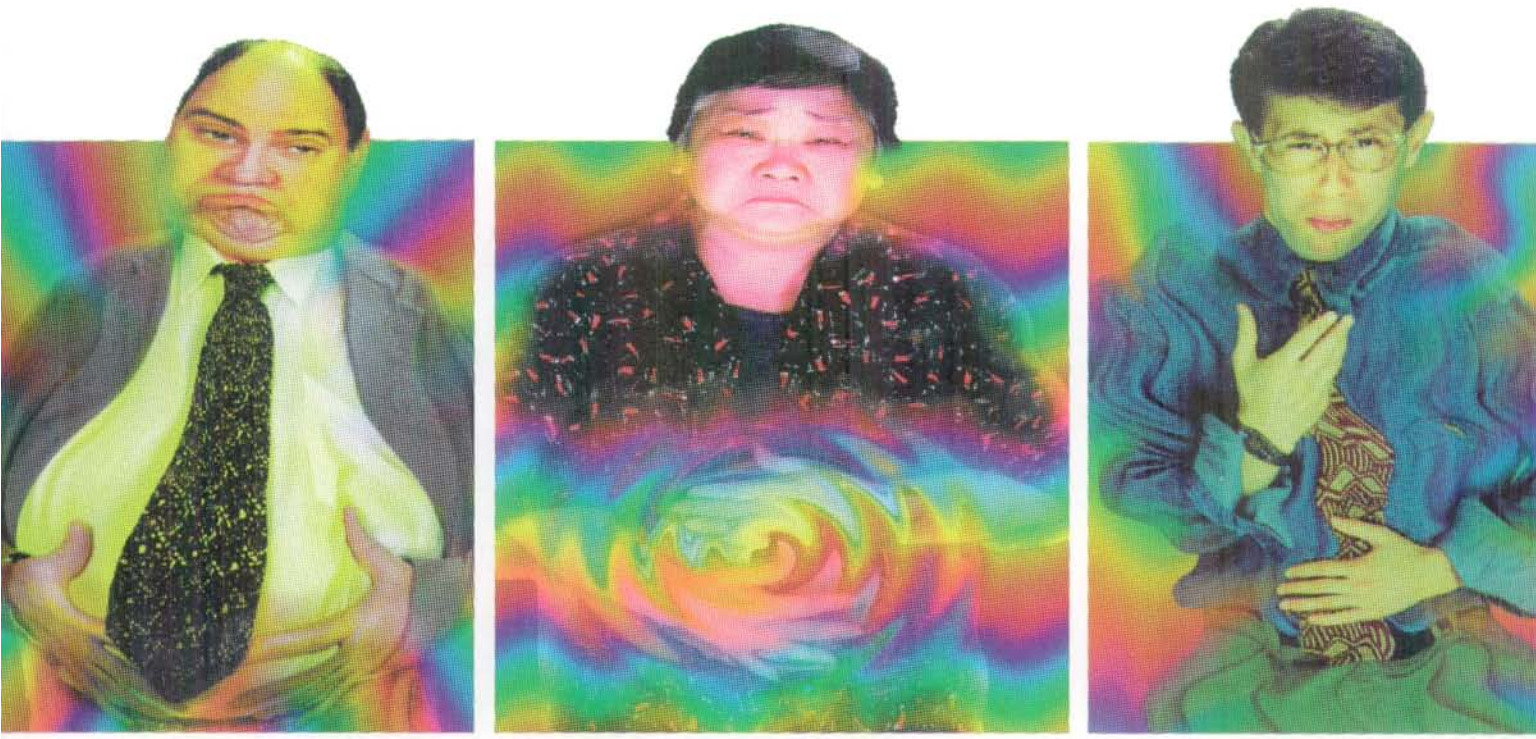
Diabetic gastropathy can be hard to stomach...



Just ask your patients.

Up to 47% of patients with diabetes experience upper gastrointestinal (GI) symptoms[1,2]—yet may not tell their doctors. The symptoms of diabetic gastropathy include bloating, early satiety, abdominal pain, nausea, and vomiting[3] and are prevalent in patients with both type 1 and type 2 diabetes.[1] Unfortunately, in most cases, patients don't make the connection between upper GI symptoms and their diabetes. So these symptoms may often go unreported and consequently undertreated.

Upper GI symptoms may diminish quality of life for patients with diabetes. The fact is, upper GI symptoms add to the disruptive and disabling nature of diabetes. They may even diminish quality of life for patients with diabetes. Patients with diabetes need special care, and their stomachs may need special care as well.

Janssen Pharmaceutica is developing new therapies specifically for patients with diabetes who suffer from upper GI symptoms. Diabetic gastropathy presents another obstacle to lives already complicated by an intrusive disorder. Increased awareness of diabetic gastropathy and its symptoms is the first step toward improving quality of life for millions of people with diabetes.

References:
1. The Gallup Organization. Gastrointestinal Symptoms Among Diabetics. June, 1995. 2. Kawagishi T, Nishizawa Y, Emoto M, et al. Gastric myoelectrical activity in patients with diabetes: role of glucose control and autonomic nerve function. *Diabetes Care*. 1997;20(5):848-854. 3. Drenth JPH, Engels LGJB. Diabetic gastroparesis: a critical reappraisal of new treatment strategies. *Drugs*. 1992;44(4):537-553.

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February 1998

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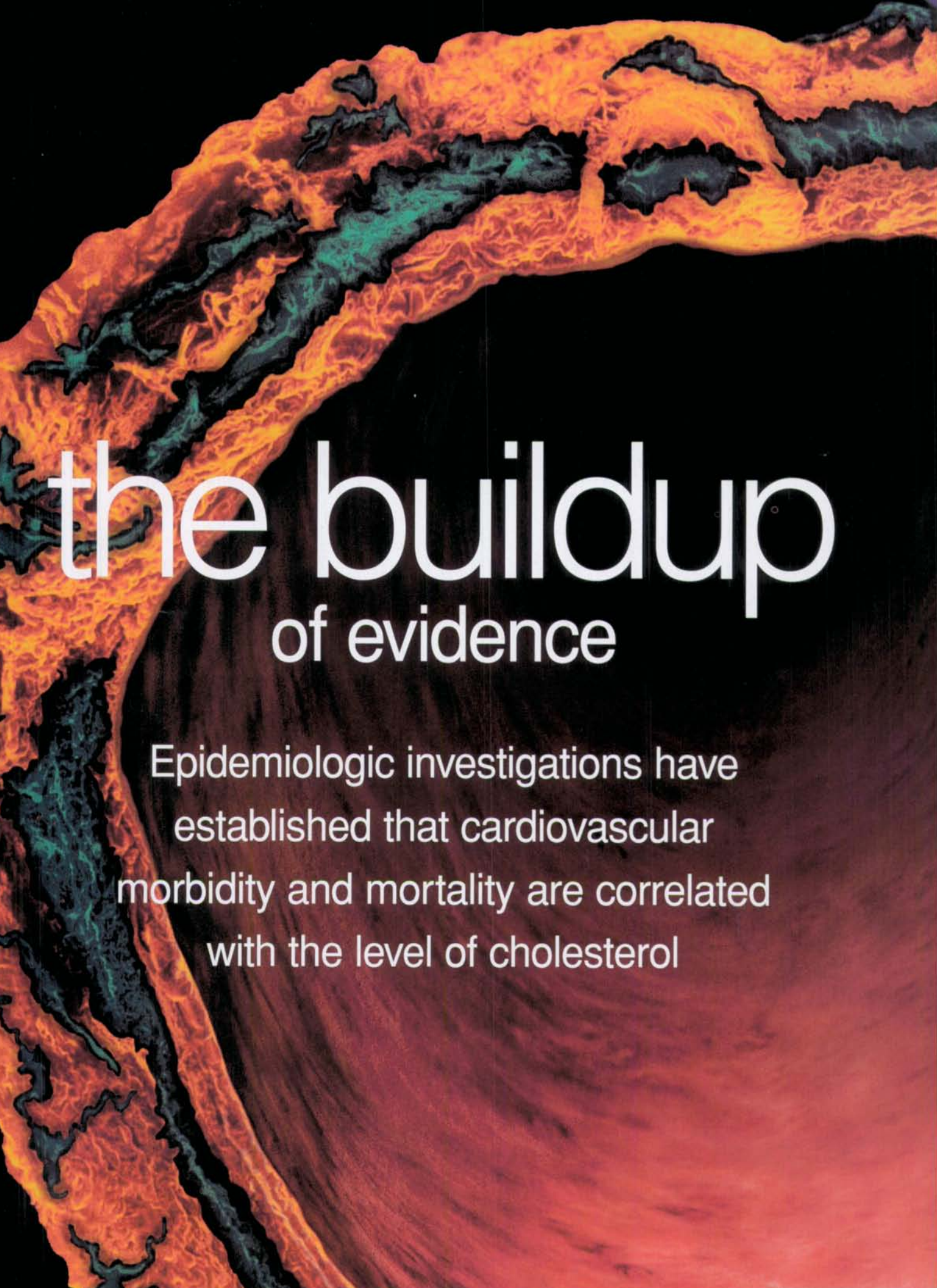
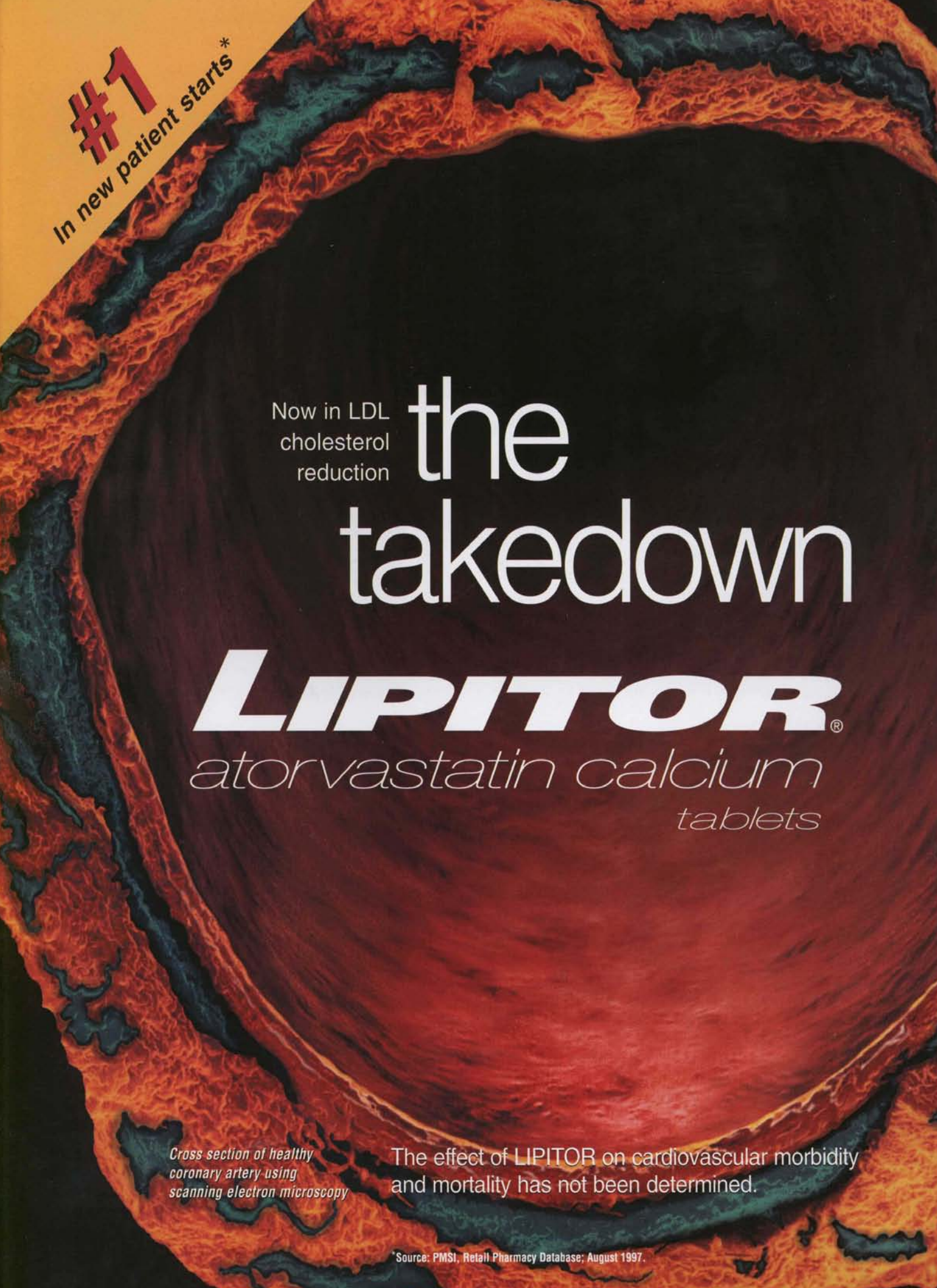
Reference: 1. Data on file, Novo Nordisk Pharmaceuticals, Inc.


the buildup
of evidence
Epidemiologic investigations have
established that cardiovascular
morbidity and mortality are correlated
with the level of cholesterol


#1
In new patient starts*
Now in LDL cholesterol reduction
the takedown
LIPITOR®
atorvastatin calcium
tablets
Cross section of healthy coronary artery using scanning electron microscopy
The effect of LIPITOR on cardiovascular morbidity and mortality has not been determined.
*Source: PMSI, Retail Pharmacy Database; August 1997.

Results across key parameters

Lowers LDL-C **39%** to **60%**

Lowers triglycerides **19%** to **37%**

Raises HDL-C **5%** to **9%**

based on mean changes in placebo-controlled trials of LIPITOR 10 to 80 mg

More power than Zocor®, Pravachol®, and Mevacor®

in head-to-head trials to lower LDL-C at starting doses[1-3]*

Versatility in a broad range of hypercholesterolemic patients

In clinical trials, the most common adverse events were constipation, flatulence, dyspepsia, and abdominal pain.

As with any statin, it is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter.

LIPITOR is contraindicated in patients with hypersensitivity to any component of this medication; in patients with active liver disease or unexplained persistent elevations of serum transaminases; in women during pregnancy and in nursing mothers.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of creatine phosphokinase (CPK). Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

*The impact on clinical outcomes of the differences in lipid-altering effects between these treatments is not known. This statement does not compare the effects of LIPITOR 10 mg and higher doses of simvastatin, pravastatin, and lovastatin.

New

LIPITOR™

atorvastatin calcium

tablets

TAKING CHOLESTEROL TO NEW LOWS

Please see brief summary of prescribing information on last page.

References: 1. Dart A, Jerums G, Nicholson G, et al. A multicenter, double-blind, one-year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia. *Am J Cardiol.* 1997;80:39-44. **2.** Bertolini S, Bon GB, Campbell LM, et al. Efficacy and safety of atorvastatin compared to pravastatin in patients with hypercholesterolemia. *Atherosclerosis.* 1997;130:191-197. **3.** Davidson M, McKenney J, Stein E, et al, for the Atorvastatin Study Group I. Comparison of one-year efficacy and safety of atorvastatin versus lovastatin in primary hypercholesterolemia. *Am J Cardiol.* 1997;79:1475-1481.

LIPITOR® (Atorvastatin Calcium) Tablets
Brief Summary of Prescribing Information

CONTRAINDICATIONS: Active liver disease or unexplained persistent elevations of serum transaminases. Hypersensitivity to any component of this medication. **Pregnancy and Lactation:** Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS: Liver Dysfunction — HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.** One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin. **It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically (eg, semiannually) thereafter.** Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see CONTRAINDICATIONS). **Skeletal Muscle — Rhabdomyolysis with acute renal failure secondary to myoglobinuria has been reported with other drugs in this class.** Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. **Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).**

PRECAUTIONS: General — Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in full prescribing information). **Information for Patients** — Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. **Drug Interactions** — The risk of myopathy during treatment with other drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, Skeletal Muscle). ***Antacid:*** When atorvastatin and Maalox® TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered. ***Antipyrine:*** Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected. ***Colestipol:*** Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone. ***Cimetidine:*** Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine. ***Digoxin:*** When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately. ***Erythromycin:*** In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, Skeletal Muscle). ***Oral Contraceptives:*** Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin. ***Warfarin:*** Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment. ***Other Concomitant Therapy:*** In clinical studies, atorvastatin was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted. **Endocrine Function** — HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine. **CNS Toxicity** — Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day. CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. **Carcinogenesis, Mutagenesis, Impairment of Fertility** — In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose. A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose. *In vitro,* atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli,* the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test. Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years. **Pregnancy: Pregnancy Category X — See CONTRAINDICATIONS.** Safety in pregnant women has not been established. Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2). In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. LIPITOR should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking LIPITOR, it should be discontinued and the patient advised again as to the potential hazards to the fetus. **Nursing Mothers:** Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see CONTRAINDICATIONS). **Pediatric Use:** Treatment experience in a pediatric population is limited to doses of LIPITOR up to 80 mg/day for 1 year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients. None of these patients was below 9 years of age. **Geriatric Use:** Treatment experience in adults age ≥70 years with doses of LIPITOR up to 80 mg/day has been evaluated in 221 patients. The safety and efficacy of LIPITOR in this population were similar to those of patients <70 years of age.

ADVERSE REACTIONS: LIPITOR is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin. The most frequent adverse events thought to be related to atorvastatin were constipation, flatulence, dyspepsia, and abdominal pain. **Clinical Adverse Experiences:** Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment:

Adverse Events in Placebo-Controlled Studies (% of Patients)

BODY SYSTEM Adverse Event	Placebo N = 270	Atorvastatin 10 mg N = 863	Atorvastatin 20 mg N = 36	Atorvastatin 40 mg N = 79	Atorvastatin 80 mg N = 94
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

The following adverse events were reported, regardless of causality assessment in patients treated with atorvastatin in clinical trials. The events in italics occurred in ≥2% of patients and the events in plain type occurred in <2% of patients.

Body as a Whole: *Chest pain,* face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema. ***Digestive System:*** *Nausea,* gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice. ***Respiratory System:*** *Bronchitis, rhinitis,* pneumonia, dyspnea, asthma, epistaxis. ***Nervous System:*** *Insomnia, dizziness,* paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia. ***Musculoskeletal System:*** *Arthritis,* leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis. ***Skin and Appendages:*** Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer. ***Urogenital System:*** *Urinary tract infection,* urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage. ***Special Senses:*** Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion. ***Cardiovascular System:*** Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension. ***Metabolic and Nutritional Disorders:*** *Peripheral edema,* hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia. ***Hemic and Lymphatic System:*** Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia. ***Postintroduction Reports:*** Adverse events associated with LIPITOR that have been received since market introduction, that are not listed above, and that may have no casual relationship to drug include the following: angioneurotic edema.

OVERDOSAGE: There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

Caution – Federal law prohibits dispensing without prescription.

Consult package insert before prescribing LIPITOR® (Atorvastatin Calcium) Tablets.

Revised November 1997 0155G023

PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA
MADE IN GERMANY

Marketed by:
PARKE-DAVIS
Div of Warner-Lambert Co and
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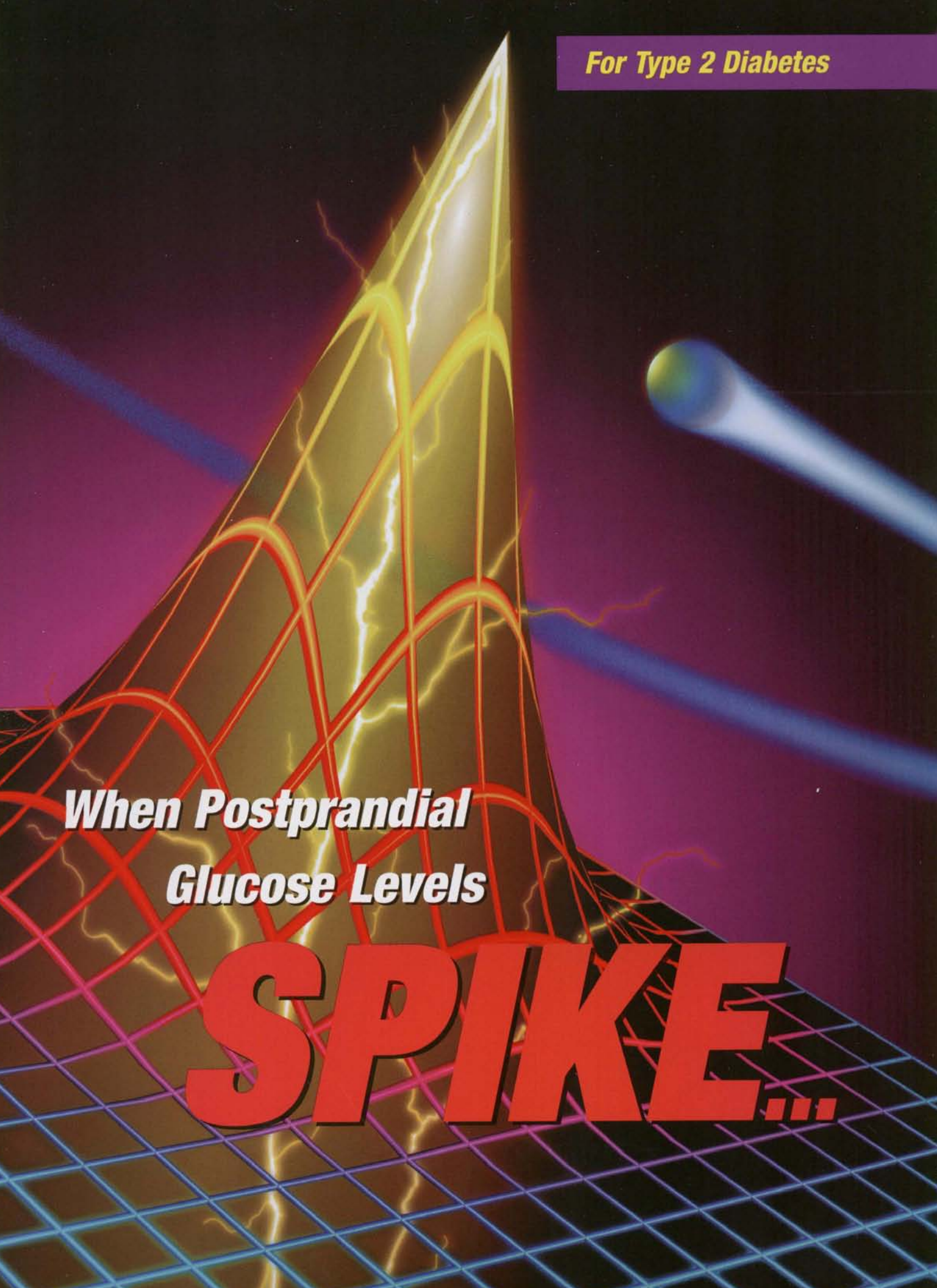
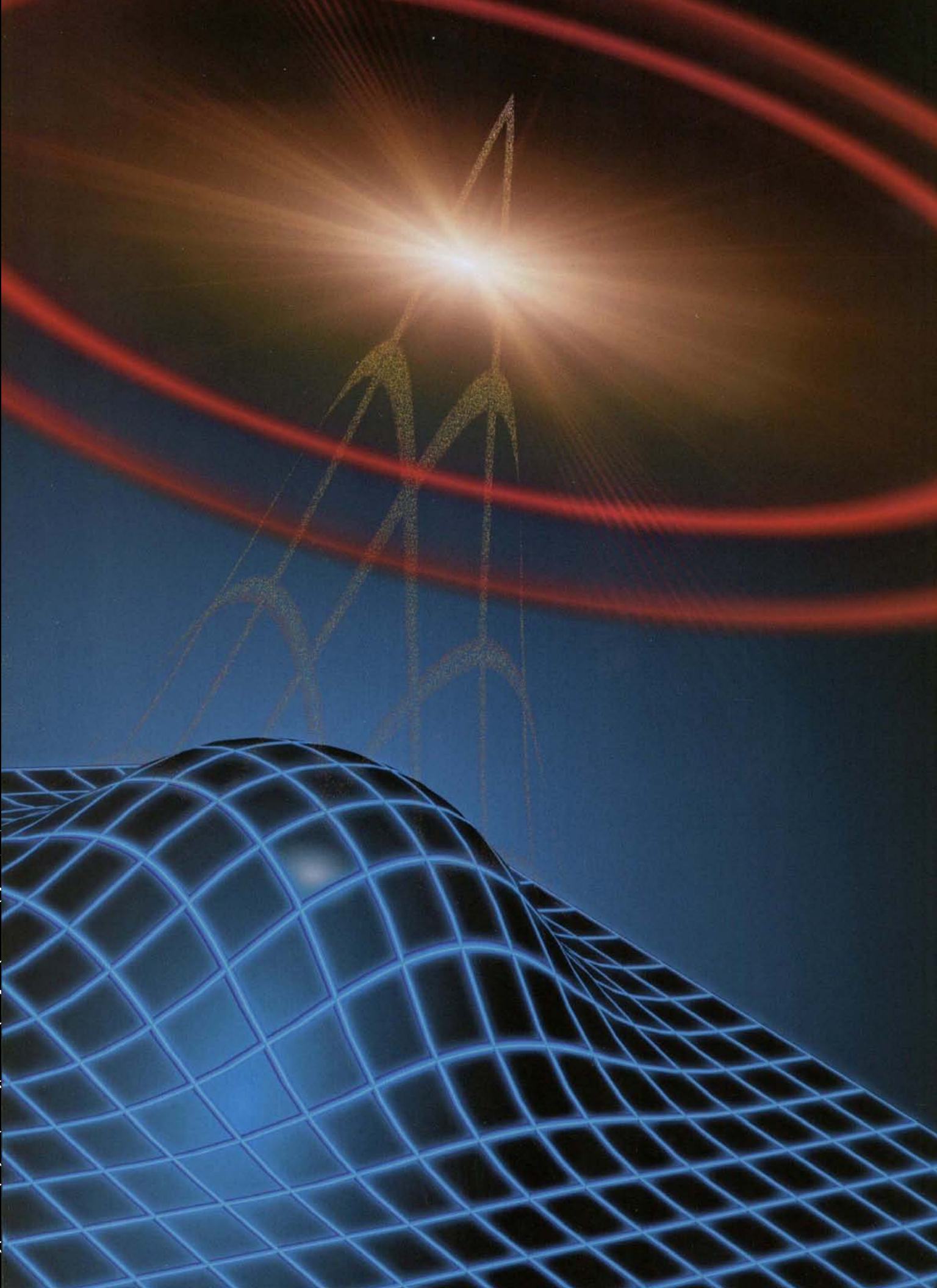
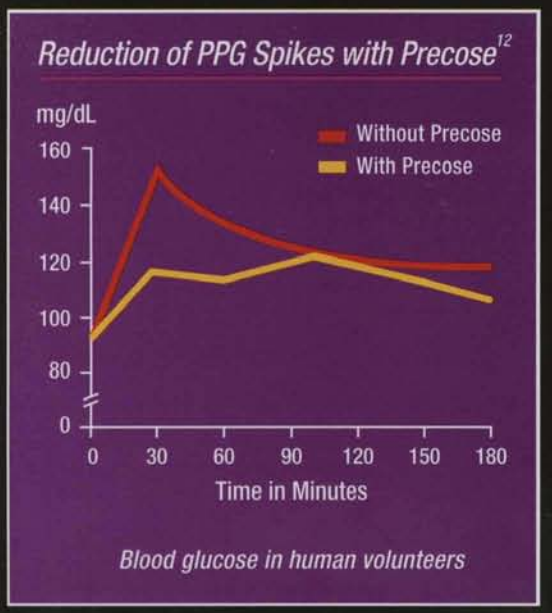

For Type 2 Diabetes
When Postprandial
Glucose Levels
SPIKE...



STRIKE the Spike

Target Hazardous Postprandial Glucose Spikes with Precose



Striking Performance

- Unique, nonsystemic mode of action reduces hazardous postprandial glucose (PPG) spikes and HbA1c for effective glycemic control[1,2,3]

Striking Benefit

- Reducing PPG spikes may protect against micro- and macrovascular complications[2,4-9]

Striking Indication

- First-line therapy for newly diagnosed patients; adjunct therapy for patients on sulfonylureas in need of additional glycemic control[1,10]

Striking Contrast

- Precose does not cause:
  - hypoglycemia[2]
  - hyperinsulinemia[2]
  - weight gain[1,2]
  - lactic acidosis[11]

25 mg, 50 mg, 100 mg

Precose®
(acarbose tablets)

PPG reduction from the first strike

Please see brief summary of Prescribing Information on the last page of this advertisement.

STRIKE the Spike with Precose

New 25 mg Tablets

- *Reduces PPG spikes*
- *PPG control may protect against micro- and macrovascular complications*
- *Effective mono- and combination therapy*
- *Established safety profile*

Each scheduled dose of Precose should be taken with the first bite of the meal

Initial starting dose: 25 mg tid

Recommended alternate titration dosage for enhanced patient tolerance		*25 mg* qd *weeks 1-2*
		*25 mg* bid *weeks 3-4*
		*25 mg* tid *weeks 5-12*
Maintenance dose		*50 mg* tid
*Maximum dose**		*100 mg* tid

*50 mg *tid* for patients ≤ 132 lbs.
100 mg *tid* for patients > 132 lbs.

Safety Profile[1]

Precose is contraindicated in patients with inflammatory bowel disease, colonic ulceration, or partial intestinal obstruction. The most common side effects associated with Precose are flatulence, abdominal pain, and diarrhea.

Please see brief summary of Prescribing Information on the last page of this advertisement.

Bayer

Pharmaceutical Division

25 mg, 50 mg, 100 mg

Precose®
(acarbose tablets)

PPG reduction from the first strike

25mg, 50mg, 100mg

Precose®

(acarbose tablets)

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.

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Pharmaceutical Division

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Glucose Control

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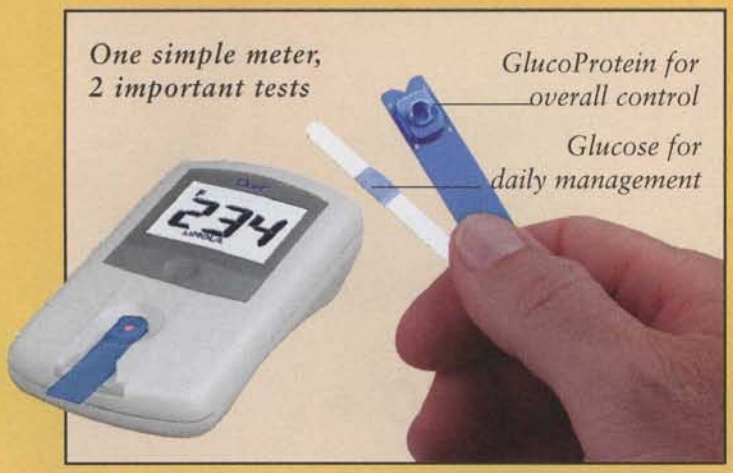
Featuring the first ever stat test for GlucoProtein™ (fructosamine).

New! GlucoProtein Test. A major breakthrough in diabetes management. Just one fingerstick can indicate if a diabetes treatment plan is resulting in good control or poor control.

Glucose Control. You want to avoid disease complications by maintaining blood glucose levels in the normal range. But how do you know if your treatment plan is working? Patients' glucose logs don't always give the whole story. GlucoProtein tests can complete the picture. Each test gives the average of ***continuous*** glucose levels over the prior 2-3 weeks.



For you, for your patients

- lab test accuracy
- inexpensive
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A Complete System. GlucoProtein tests and glucose tests go together. The perfect pairing. Only the new Duet Glucose Control System performs both tests. Duet Test Strips monitor glucose. GlucoProtein Test Strips monitor overall control. Both tests follow the same simple fingerstick procedure. Just add blood and await results.

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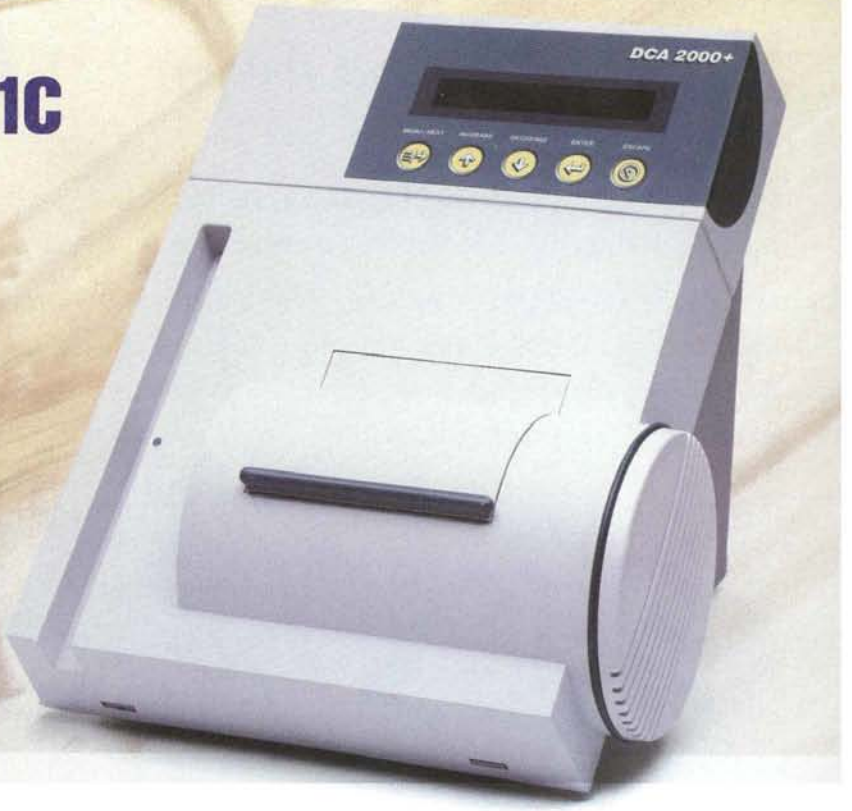
HbA_{1c}

microalbumin creatinine



Right *now*... while your patient is in your office

Hemoglobin A_{1c} and Microalbumin/Creatinine ratio: Accurate results in just minutes!

Results from the 9-year DCCT (Diabetes Control and Complications Trial) conclude that controlling blood glucose levels reduces risk.[1]

Reduce the risk by monitoring HbA_{1c} and microalbumin levels with the DCA 2000+ Analyzer. With the totally self-contained test reagent cartridges, you eliminate all reagent preparation, mixing, and handling. The sample collection tube is an integral part of the unique reagent cartridge for optimal convenience.

There's no costly, time-consuming wet calibration. All instructions, status, and testing information appear on the screen.

DCA 2000®+ Analyzer

And up to 16 results are stored in memory for convenient recordkeeping. Review patient data during the visit and adjust the blood glucose control regimen as appropriate.

Prevent complications. In-office testing with the DCA 2000+ Analyzer gives you results you can act on. Now.

For more information about the DCA 2000+ Analyzer, contact your local Bayer Representative. And visit us on the Internet: http://www.bayerdiag.com

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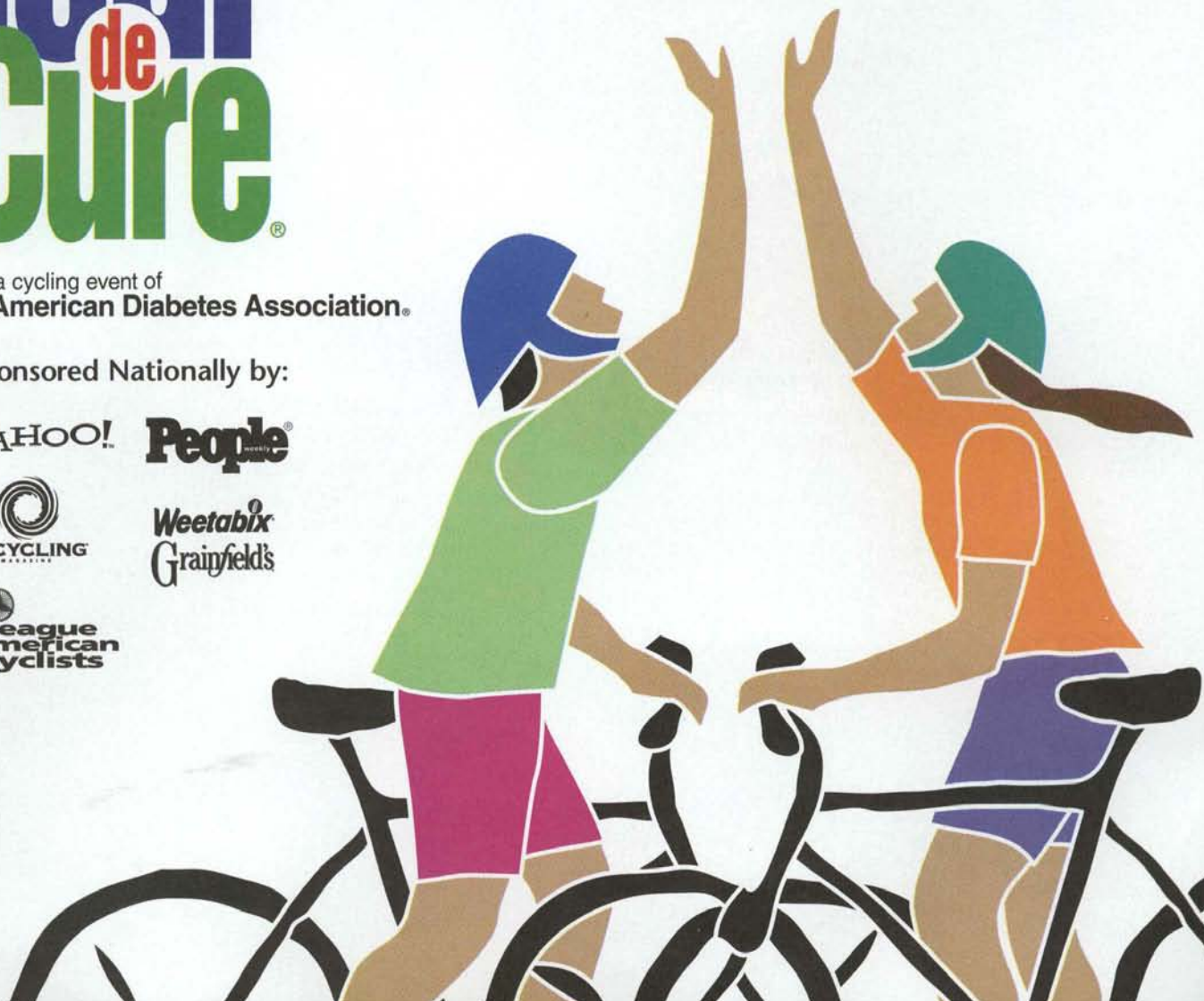

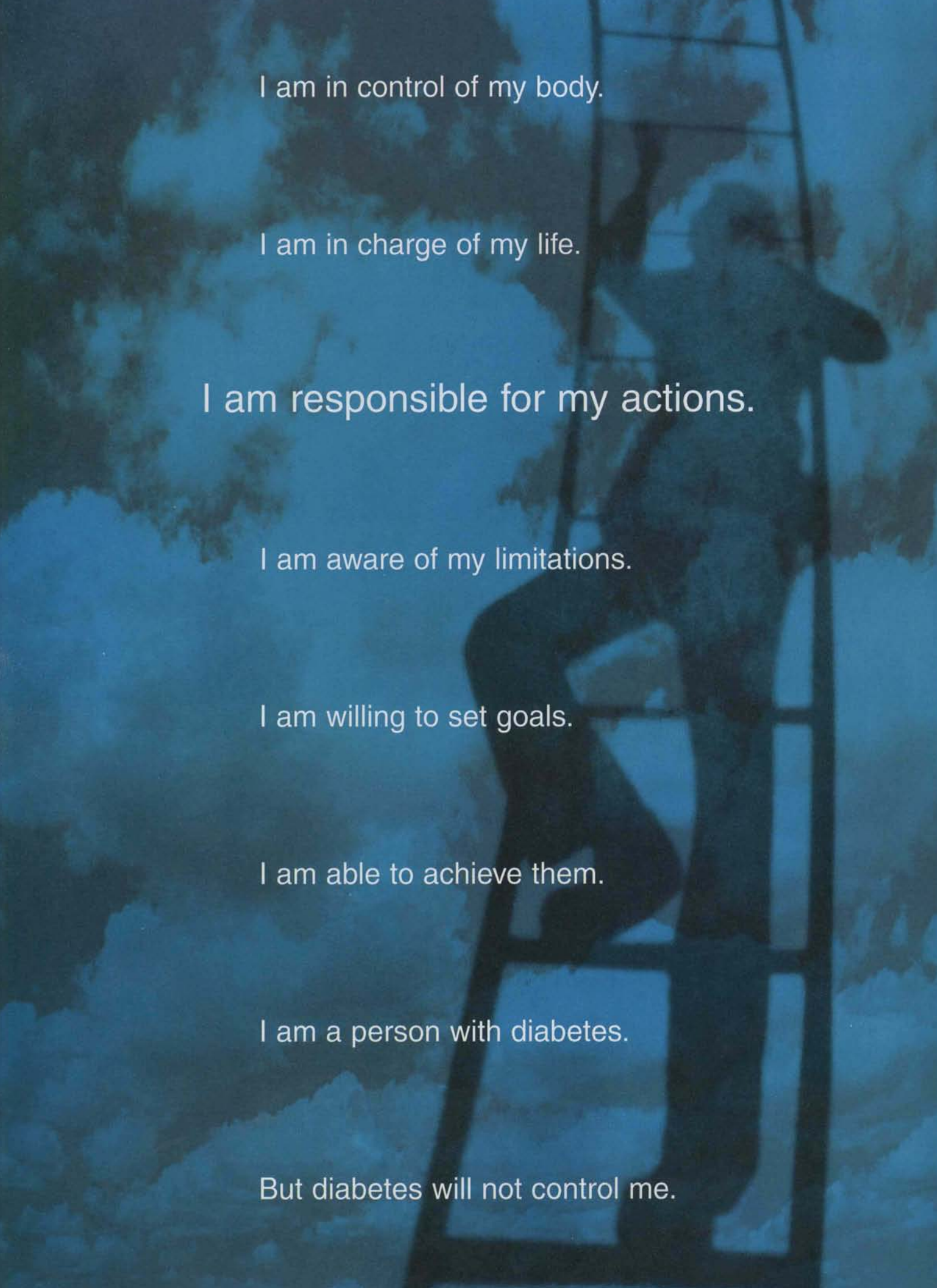

I am in control of my body.

I am in charge of my life.

I am responsible for my actions.

I am aware of my limitations.

I am willing to set goals.

I am able to achieve them.

I am a person with diabetes.

But diabetes will not control me.

The Accu-Chek® SoftClix® lancet device makes blood glucose testing virtually pain free.

Diabetes is a part of your patients' lives. But we don't think it should run their lives. Whether it's our line of discreet, convenient products for monitoring their blood sugar, or our 24-hour Medical Services Center Line to answer any questions, they can count on Accu-Chek to make living with diabetes a little easier.

ACCU-CHEK

Live life. We'll fit in.

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THE ELUSIVE GOAL OF GOOD CONTROL

THE REALITIES OF GOOD GLYCEMIC CONTROL IN TYPE 2 DIABETES

Although long-term hyperglycemia is known to cause serious complications,[1,2] good control is clinically practical only if it can be achieved without a consequential risk of recurring hypoglycemic episodes.[3] Because of the safety concerns in oral hypoglycemic therapy, good control of type 2 diabetes has remained an elusive goal. Shorter-acting compounds may be preferred over longer-acting agents.[4]

THE NEED FOR A MORE PHYSIOLOGIC APPROACH

While most patients with type 2 diabetes retain some insulin secretory capacity, they also exhibit a decreased insulin secretory response to glucose.[4] Studies show that both obese and nonobese patients experience a delayed and decreased rise in plasma insulin following meals, when their plasma glucose levels are high.[4] Agents that are rapidly absorbed and quickly eliminated could achieve better control without increasing the risk of hypoglycemia when fasting or of between-meal hyperinsulinemia.[5,6] Oral hypoglycemic agents that make the most of beta-cell activity when patients need it the most—at mealtime—would be logical therapeutic options.[5,6]

MEETING THE CHALLENGE OF ORAL GLUCOSE LOADS

When diet and exercise alone fail to improve blood glucose levels, therapy that augments meal-stimulated insulin release could result in a dose-dependent decrease in plasma glucose levels.[6,7] Adopting a more physiologic strategy such as this could also help avoid constant stimulation of the beta cells and could lower the risk of hypoglycemia—a significant distinction from traditional oral hypoglycemic agents.[6,7]

NEW GUIDELINES FOR TYPE 2 DIABETES

An effort to save more Americans from the serious complications of diabetes has led to the development of new guidelines for diagnosis of diabetes, based on lower blood glucose measures of hyperglycemia.[1,8]

An international Expert Committee, sponsored by the American Diabetes Association, reported new diagnostic criteria in June of 1997. Today, any patient with a fasting plasma glucose* (FPG) reading of ≥ 126 mg/dL on two separate occasions is now considered to have type 2 diabetes. Even a person with a fasting glucose reading over 110 mg/dL is considered to be at risk.[1,8]

*Fasting is defined as no caloric intake for at least 8 hours.

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Novo Nordisk

123594 February 1998

Introducing an innovation to help promote healing

For diabetic neuropathic foot ulcers...*

NEW REGRANEX® GEL 0.01%
(becaplermin)

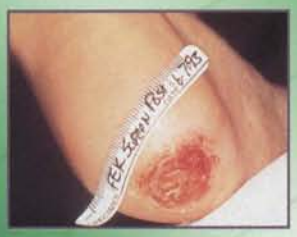
* REGRANEX Gel is indicated for diabetic neuropathic foot ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. REGRANEX Gel is an adjunct to, and not a substitute for, good wound care, which includes initial sharp debridement, pressure relief, and infection control.

Please see full Prescribing Information, a brief summary of which appears on the last page of this advertisement.

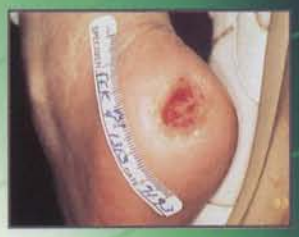
HELP PROMOTE HEALING

- REGRANEX Gel is the first and only recombinant platelet-derived growth factor (PDGF)
- REGRANEX Gel enhances the formation of granulation tissue
- REGRANEX Gel is recombinant (not blood derived) and readily available by prescription

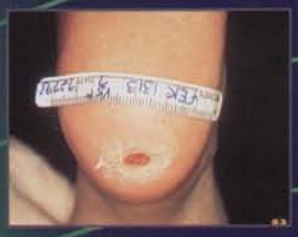
Case study results



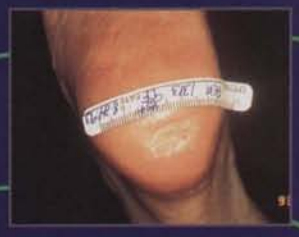
After debridement, prior to therapy with REGRANEX Gel



After 2 weeks of REGRANEX Gel plus good wound care

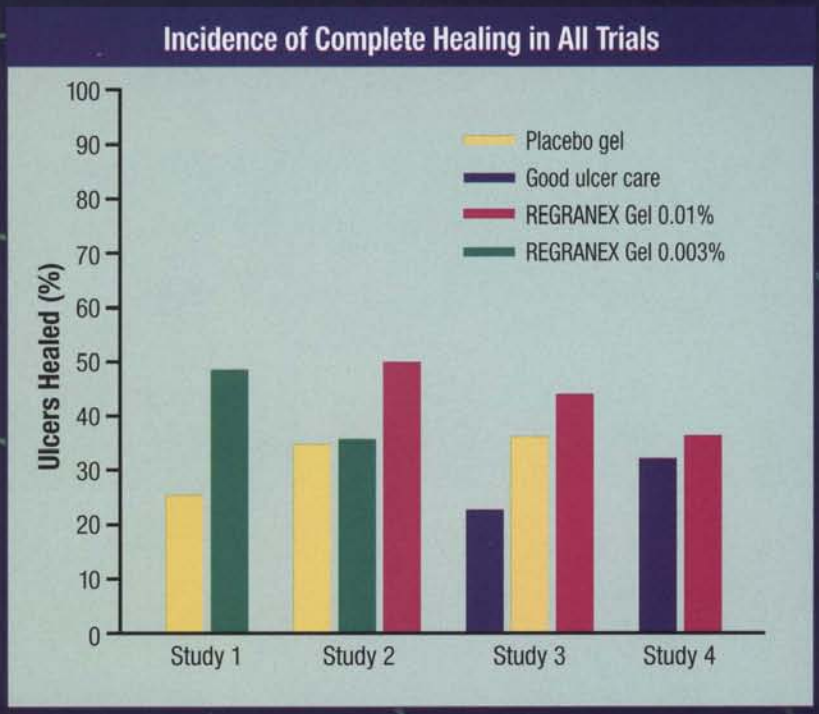


After 5 weeks of REGRANEX Gel plus good wound care



After 10 weeks of REGRANEX Gel plus good wound care

When combined with good wound care, REGRANEX Gel increased the incidence of complete healing



NEW REGRANEX® GEL 0.01% (becaplermin)

Helps Promote Healing...Actively

Systemic and local adverse events comparable to placebo gel or good wound care alone.

REGRANEX Gel has not been studied in the treatment of diabetic neuropathic ulcers that do not extend into the subcutaneous tissue or beyond (Stage I or II, IAET staging classification). The efficacy of REGRANEX Gel for the treatment of nondiabetic ulcers is under evaluation. REGRANEX Gel is contraindicated in patients with known neoplasms at the site of application. REGRANEX Gel is contraindicated in patients with known hypersensitivity to any component of this product (eg, parabens). Erythematous rashes occurred in 2% of patients treated with REGRANEX Gel. REGRANEX Gel should not be used in wounds that close by primary intention.

Please see full Prescribing Information, a brief summary of which appears on the last page of this advertisement.

Good wound care is critical to success

- Adequate oxygen perfusion of the wound
- Initial and ongoing wound assessment
- Initial and ongoing debridement
- Off-loading of pressure on wound
- Systemic treatment of infection
- Moist dressings changed twice a day
- Proper nutrition and hydration

- For more information, call our professional support line at **1-888-REGRANEX**
- Please visit our website at **www.regranex.com**

NEW
REGRANEX® GEL 0.01%
(becaplermin)
Helps Promote Healing...Actively

Please see full Prescribing Information, a brief summary of which appears below.

IMPORTANT NOTE – This information is a BRIEF SUMMARY of the complete prescribing information provided with the product and therefore should not be used as the basis for prescribing the product. This summary was prepared by deleting from the complete prescribing information certain text, tables, and references. The physician should be thoroughly familiar with the complete prescribing information before prescribing the product.

REGRANEX® Gel contains becaplermin, a recombinant human platelet-derived growth factor (rhPDGF-BB) for topical administration.

INDICATIONS AND USAGE
REGRANEX Gel is indicated for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. When used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp debridement, pressure relief and infection control, REGRANEX Gel increases the incidence of complete healing of diabetic ulcers.

The efficacy of REGRANEX Gel for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue (Stage I or II, IAET staging classification) or ischemic diabetic ulcers has not been evaluated.

CONTRAINDICATIONS
REGRANEX Gel is contraindicated in patients with:
– known hypersensitivity to any component of this product (e.g., parabens);
– known neoplasm(s) at the site(s) of application.

WARNINGS
REGRANEX Gel is a non-sterile, low bioburden preserved product. Therefore, it should not be used in wounds that close by primary intention.

PRECAUTIONS
For external use only.

If application site reactions occur, the possibility of sensitization or irritation caused by parabens or m-cresol should be considered.

The effects of becaplermin on exposed joints, tendons, ligaments, and bone have not been established in humans. In pre-clinical studies, rats injected at the metatarsals with 3 or 10 µg/site (approximately 60 or 200 µg/kg) of becaplermin every other day for 13 days displayed histological changes indicative of accelerated bone remodeling consisting of periosteal hyperplasia and subperiosteal bone resorption and exostosis. The soft tissue adjacent to the injection site had fibroplasia with accompanying mononuclear cell infiltration reflective of the ability of PDGF to stimulate connective tissue growth.

Information for Patients
Patients should be advised that:
– hands should be washed thoroughly before applying REGRANEX Gel;
– the tip of the tube should not come into contact with the ulcer or any other surface; the tube should be recapped tightly after each use;
– a cotton swab, tongue depressor, or other application aid should be used to apply REGRANEX Gel;
– REGRANEX Gel should only be applied once a day in a carefully measured quantity (see Dosage and Administration section). The measured quantity of gel should be spread evenly over the ulcerated area to yield a thin continuous layer of approximately 1/16 of an inch thickness. The measured length of the gel to be squeezed from the tube should be adjusted according to the size of the ulcer. The amount of REGRANEX Gel to be applied daily should be recalculated at weekly or biweekly intervals by the physician or wound care giver;

Step-by-step instructions for application of REGRANEX Gel are as follows:

- Squeeze the calculated length of gel on to a clean, firm, non-absorbable surface, e.g., wax paper.
- With a clean cotton swab, tongue depressor, or similar application aid, spread the measured REGRANEX Gel over the ulcer surface to obtain an even layer.
- Cover with a saline moistened gauze dressing.

– after approximately 12 hours, the ulcer should be gently rinsed with saline or water to remove residual gel and covered with a saline-moistened gauze dressing (without REGRANEX Gel);
– it is important to use REGRANEX Gel together with a good ulcer care program, including a strict non-weight-bearing program;
– excess application of REGRANEX Gel has not been shown to be beneficial;
– REGRANEX Gel should be stored in the refrigerator. Do not freeze REGRANEX Gel;
– REGRANEX Gel should not be used after the expiration date on the bottom, crimped end of the tube.

Drug Interactions
It is not known if REGRANEX Gel interacts with other topical medications applied to the ulcer site. The use of REGRANEX Gel with other topical drugs has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Becaplermin was not genotoxic in a battery of *in vitro* assays, (including those for bacterial and mammalian cell point mutation, chromosomal aberration, and DNA damage/repair). Becaplermin was also not mutagenic in an *in vivo* assay for the induction of micronuclei in mouse bone marrow cells.

Carcinogenesis and reproductive toxicity studies have not been conducted with REGRANEX Gel.

Pregnancy: Category C
Animal reproduction studies have not been conducted with REGRANEX Gel. It is also not known whether REGRANEX Gel can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. REGRANEX Gel should be given to pregnant women only if clearly needed.

Nursing Mothers
It is not known whether becaplermin is excreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when REGRANEX Gel is administered to nursing women.

Pediatric Use
Safety and effectiveness of REGRANEX Gel in pediatric patients below the age of 16 years have not been established.

ADVERSE REACTIONS
Patients receiving REGRANEX Gel, placebo gel, and good ulcer care alone had a similar incidence of ulcer-related adverse events such as infection, cellulitis, or osteomyelitis. However, erythematous rashes occurred in 2% of patients treated with REGRANEX Gel and placebo, and none in patients receiving good ulcer care alone. The incidence of cardiovascular, respiratory, musculoskeletal and central and peripheral nervous system disorders was not different across all treatment groups. Mortality rates were also similar across all treatment groups. Patients treated with REGRANEX Gel did not develop neutralizing antibodies against becaplermin.

Caution: Federal (USA) law prohibits dispensing without prescription.

U.S. Patent #5,457,093

ORTHO-McNEIL

Distributed by:
ORTHO-McNEIL
PHARMACEUTICAL, INC.
Raritan, New Jersey 08869

Manufactured by:
OMJ Pharmaceuticals, Inc.
U.S. License No. 1196
San German, Puerto Rico 00683

Becaplermin Concentrate provided by: Chiron Corp.,
U.S. License No. 1106, Emeryville, CA 94608

 Revised February 1998 635-10-240-2B

ORTHO-McNEIL

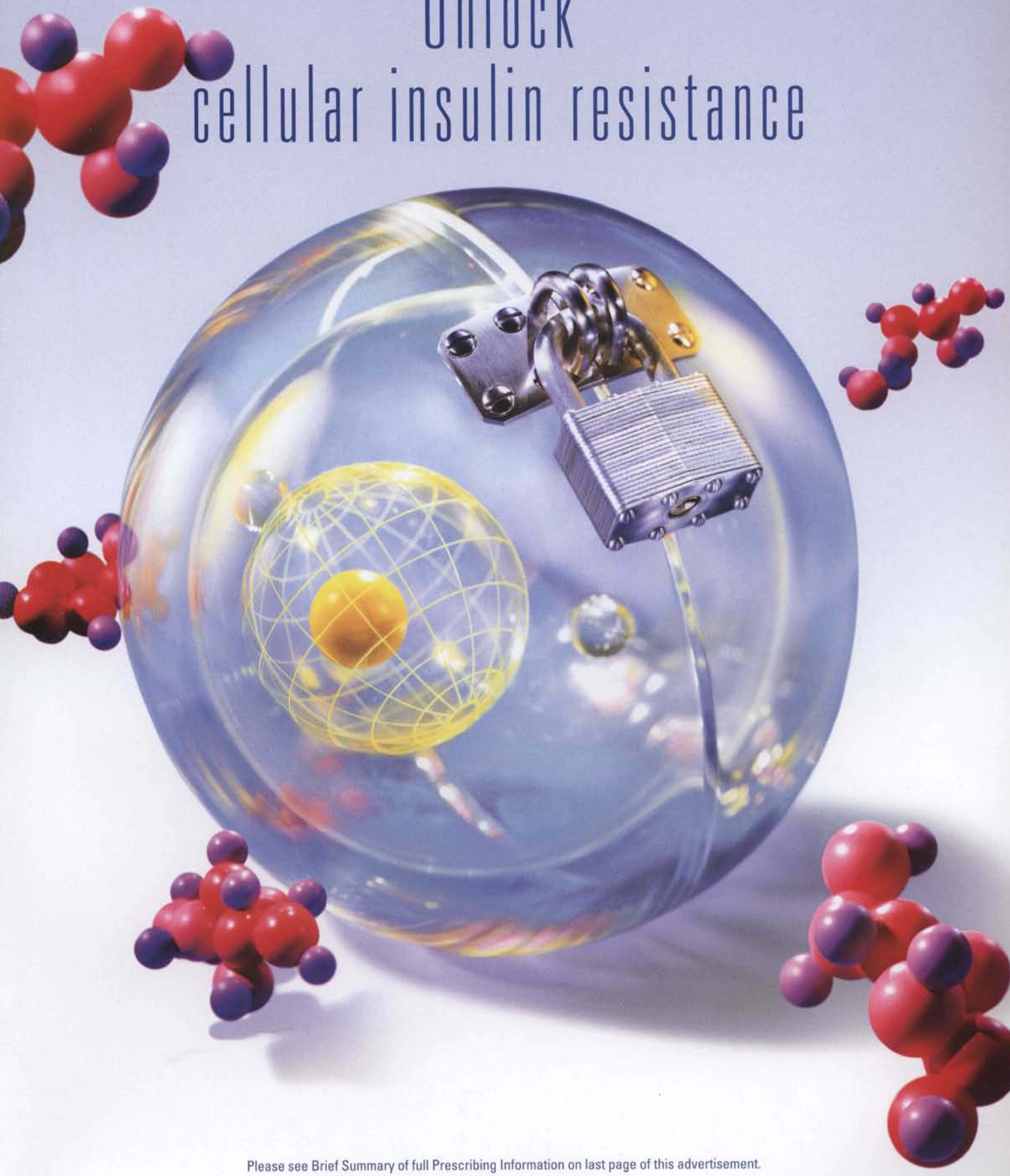
TRANSFORMING WOUND CARE TO WOUND HEALING

Ortho-McNeil Pharmaceutical, Inc.
Raritan, NJ 08869-0602

 02J2881W 3/98

IN TYPE 2 DIABETES

Unlock cellular insulin resistance



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

New synergy

in combination with sulfonylureas

Synergy that results in significant reductions in HbA_{1c}

• In a clinical trial at 1 year, Rezulin (600 mg/day), given in combination with micronized glyburide, reduced HbA_{1c} by **2.7***

Synergy that helps reach ADA targets

• In the same study at 1 year,
60% of patients achieved $HbA_{1c} \leq 8\%$
41% of patients achieved $HbA_{1c} \leq 7\%$

Synergy that works with diet and exercise at every stage

• Indicated for concomitant use with a sulfonylurea or insulin or as monotherapy, as an adjunct to diet and exercise, in type 2 diabetes

The first and only PPAR-gamma Activator

REZULIN®

Unlocks insulin resistance

* Rezulin 600 mg and 12 mg micronized glyburide qd vs glyburide alone. This presentation represents the results of patients receiving the maximum dose of Rezulin. Please refer to the package insert for results of patients receiving lower doses.

Rezulin may be used concomitantly with a sulfonylurea or insulin to improve glycemic control. Rezulin, as monotherapy, is indicated as an adjunct to diet and exercise to lower blood glucose in patients with type 2 diabetes. Rezulin should not be used as monotherapy in patients previously well controlled on sulfonylurea therapy. For patients inadequately controlled with a sulfonylurea alone, Rezulin should be added to, not substituted for, the sulfonylurea.

Management of type 2 diabetes should also include diet control, weight loss, and exercise, which are essential for proper treatment.

In a clinical study with Rezulin in combination with glyburide, these improvements in glycemic control were associated with mean weight gains of 5.8 to 13.1 pounds. To eliminate weight as a confounding factor in this study, patients had been instructed to follow a diet to maintain current weight. In studies of Rezulin as monotherapy, there were no clinically significant changes in weight.

Prior to initiation of Rezulin therapy, correctable causes of poor glycemic control should be sought and treated. Rezulin should not be used in type 1 diabetes or for the treatment of diabetic ketoacidosis.

Rare cases of severe idiosyncratic hepatocellular injury have been reported during marketed use (see Adverse Reactions). The hepatic injury is usually reversible, but very rare cases of hepatic failure, leading to death or liver transplant, have been reported. Injury has occurred after both short- and long-term troglitazone treatment.

It is recommended that serum transaminase levels be checked at the start of therapy, monthly for the first 6 months of therapy, every 2 months for the remainder of the first year of troglitazone therapy, and periodically thereafter. Liver function tests also should be obtained for patients at the first symptoms suggestive of hepatic dysfunction. Rezulin therapy should not be initiated if the patient exhibits clinical or laboratory evidence of active liver disease (eg, ALT >3 times the upper limit of normal) and should be discontinued if the patient has jaundice or laboratory measurements suggest liver injury (eg, ALT >3 times the upper limit of normal).

Please see following page for Brief Summary of full Prescribing Information, including **Hepatic boxed WARNING**.

ONCE-DAILY

REZULIN®

TROGLITAZONE

TABLETS

WARNINGS

Hepatic

Rare cases of severe idiosyncratic hepatocellular injury have been reported during marketed use (see ADVERSE REACTIONS). The hepatic injury is usually reversible, but very rare cases of hepatic failure, leading to death or liver transplant, have been reported. Injury has occurred after both short- and long-term troglitazone treatment.

During all clinical studies in North America, a total of 48 of 2510 (1.9%) Rezulin-treated patients and 3 of 475 (0.6%) placebo-treated patients had ALT levels greater than 3 times the upper limit of normal. Twenty of the Rezulin-treated and one of the placebo-treated patients were withdrawn from treatment. Two of the 20 Rezulin-treated patients developed reversible jaundice; one of these patients had a liver biopsy which was consistent with an idiosyncratic drug reaction. An additional Rezulin-treated patient had a liver biopsy which was also consistent with an idiosyncratic drug reaction. (See ADVERSE REACTIONS, Laboratory Abnormalities.)

It is recommended that serum transaminase levels be checked at the start of therapy, monthly for the first six months of therapy, every two months for the remainder of the first year of troglitazone therapy, and periodically thereafter. Liver function tests also should be obtained for patients at the first symptoms suggestive of hepatic dysfunction, eg, nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine. Rezulin therapy should not be initiated if the patient exhibits clinical or laboratory evidence of active liver disease (eg, ALT>3 times the upper limit of normal) and should be discontinued if the patient has jaundice or laboratory measurements suggest liver injury (eg, ALT>3 times the upper limit of normal).

BRIEF SUMMARY

Consult Package Insert for full Prescribing Information.

INDICATIONS AND USAGE

Rezulin may be used concomitantly with a sulfonylurea or insulin to improve glycemic control. Rezulin, as monotherapy, is indicated as an adjunct to diet and exercise to lower blood glucose in patients with type II diabetes (see DOSAGE AND ADMINISTRATION in Package Insert for full Prescribing Information). Rezulin should not be used as monotherapy in patients previously well-controlled on sulfonylurea therapy. For patients inadequately controlled with a sulfonylurea alone, Rezulin should be added to, not substituted for, the sulfonylurea.

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.

WARNINGS

SEE BOXED WARNING.

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.

Hypoglycemia: Patients receiving Rezulin in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia and a reduction in the dose of the concomitant agent 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).

Use in Patients With Heart Failure

Heart enlargement without microscopic changes has been observed in rodents at exposures of parent compound and active metabolite exceeding 7 times the AUC of the 400 mg human dose (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility, and Animal Toxicology). Serial echocardiographic evaluations in monkeys treated chronically at exposures at 4-9 times the human exposure to parent compound and active metabolite 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, Rezulin is not indicated unless the expected benefit is believed to outweigh the potential risk to patients with NYHA Class III or IV cardiac status.

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.

Patients who develop nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine or other symptoms suggestive of hepatic dysfunction or jaundice should immediately report these signs or symptoms to their physician.

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

Use of Rezulin can cause resumption of ovulation in women taking oral contraceptives and in patients with polycystic ovary disease. Therefore, a higher dose of an oral contraceptive or an alternative method of contraception should be considered.

Rezulin may affect other medications used in diabetic patients. Patients started on Rezulin should ask their physician to review their other medications to make sure that they are not affected by Rezulin.

Drug Interactions

Oral Contraceptives: Administration of Rezulin with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%, which could result in loss of contraception. Therefore, a higher dose of oral contraceptive or an alternative method of contraception should be considered.

Terfenadine: Coadministration of Rezulin with terfenadine decreases the plasma concentration of both terfenadine and its active metabolite by 50-70% and may result in decreased efficacy of terfenadine.

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

Glyburide: Coadministration of Rezulin and glyburide does not appear to alter troglitazone or glyburide pharmacokinetics.

Digoxin: Coadministration of Rezulin with digoxin does not alter the steady-state pharmacokinetics of digoxin.

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

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

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.

The above interactions with terfenadine and oral contraceptives suggest that troglitazone may induce drug metabolism by CYP3A4. Studies have not been performed with other drugs metabolized by this enzyme such as: astemizole, calcium channel blockers, cisapride, corticosteroids, cyclosporine, HMG-CoA reductase inhibitors, tacrolimus, triazolam, and trimetrexate. The possibility of altered safety and efficacy should be considered when Rezulin is used concomitantly with these drugs.

Patients stable on one or more of these agents when Rezulin is started should be closely monitored and their therapy adjusted as necessary.

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. No tumors of any type were increased at the low and mid doses. Plasma drug exposure based on AUC of parent compound and total metabolites at the low and mid doses was up to 24-fold higher than human exposure at 400 mg daily. The highest dose in each sex exceeded the maximum tolerated dose. 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 associated with increased tumor incidence (400 mg/kg) was associated with AUC values of parent compound and total metabolites that were at least 2-fold higher than the human exposure at 400 mg daily. No tumors of any type were increased in mice at 50 mg/kg at exposures up to 40% of that in humans at 400 mg daily, based on AUC of parent compound and total metabolites.

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 of parent compound at these doses was estimated to be 3- to 9-fold higher than the human exposure.

Animal Toxicology

Increased heart weights without microscopic changes were observed in mice and rats treated for up to 1 year at exposure (AUC) of parent and active metabolite exceeding 7 times the human AUC at 400 mg/day. These heart weight increases were reversible in 2- and 13-week studies, were prevented by coadministration of an ACE inhibitor, and 14 days of troglitazone administration to rats did not affect left ventricular performance. In the lifetime carcinogenicity studies, microscopic changes were noted in the hearts of rats but not in mice. In control and treated rats, microscopic changes included myocardial inflammation and fibrosis and karyomegaly of atrial myocytes. The incidence of these changes in drug-treated rats was increased compared to controls at twice the AUC of the 400 mg human dose.

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 in rats (parent compound) and rabbits (parent compound and active metabolite) based on AUC at these doses were up to 9-fold and 3-fold higher, respectively. 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.

ADVERSE REACTIONS

Two patients in the clinical studies developed reversible jaundice; one of these patients had a liver biopsy which was consistent with an idiosyncratic drug reaction. An additional patient had a liver biopsy which was also consistent with an idiosyncratic drug reaction. Symptoms that are associated with hepatic dysfunction have been reported, including: nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine, abnormal liver function tests (including increased ALT, AST, LDH, alkaline phosphatase, bilirubin). Also see WARNINGS.

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

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 all clinical studies in North America, a total of 48 of 2510 (1.9%) Rezulin-treated patients and 3 of 475 (0.6%) placebo-treated patients had ALT levels greater than 3 times the upper limit of normal. 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 WARNINGS).

Postintroduction Reports

Adverse events associated with Rezulin that have been reported since market introduction, that are not listed above, and for which causal relationship to drug has not been established include the following: congestive heart failure, weight gain, edema, fever, abnormal lab tests including increased CPK and creatinine, hyperglycemia, syncope, anemia, malaise.

Caution: Federal law prohibits dispensing without prescription.

December 1997

Manufactured by:
Parke Davis Pharmaceuticals, Ltd.
Vega Baja, PR 00694
For:
PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

Marketed by:
PARKE-DAVIS
Div of Warner-Lambert Co and
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Parsippany, NJ 07054 USA

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PARKE-DAVIS
Division of Warner-Lambert Company
Morris Plains, New Jersey 07950

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