THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

VOLUME 21 NUMBER 6

Diabetes Care

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American Diabetes Association.

ISSN 0149-5992

* 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.

LC150R95 Revised Oct. 1995

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THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

VOLUME 21 NUMBER 6

Diabetes Care

Diabetes Care is a journal for the health care practitioner that is intended to increase knowledge, stimulate research, and promote better management of people with diabetes. 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.

All manuscripts and other editorial correspondence should be sent to the editor, Charles M. Clark, Jr., MD, *Diabetes Care* Editorial Office, Regenstrief Institute, 6th Floor, 1001 West Tenth Street, Indianapolis, IN 46202-2859; (317) 630-6925.

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

Manuscripts should be prepared in accord with the requirements specified in the document "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," *New England Journal of Medicine* 336:309–315, 1997. "Instructions for Authors" containing specifications for manuscript preparation appears in the January and July issues.

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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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"Testing with SureStep® is about as easy as it gets. Its touchable test strip makes it almost impossible to make a mistake applying blood."

We take diabetes very personally.

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

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

SureStep®

Blood Glucose Monitoring System

For diabetes and life.

LIFESCAN INC.

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THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION
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Diabetes Care

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

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Letters

COVER: *Man in a Swing* by Gwyn Stramler, 1996. Oil, 18" × 18".

Announcing an educational symposium to be held in conjunction with the American Diabetes Association's 58th Annual Scientific Sessions in Chicago, Illinois

OBESITY AND TYPE 2 DIABETES

WEIGHT LOSS AS FIRST-LINE THERAPY

SATURDAY, JUNE 13, 1998 • 6:00AM-7:45AM

McCORMICK PLACE CONVENTION CENTER • ROOM S406

Doors open at 5:30AM for breakfast and on-site registration

CHAIR: F. XAVIER PI-SUNYER, MD

Chief–Division of Endocrinology, Diabetes and Nutrition, St. Luke's-Roosevelt Hospital Center
Professor of Medicine–Columbia University College of Physicians and Surgeons, New York, New York

Introduction
F. XAVIER PI-SUNYER, MD
Treatment of Newly Diagnosed Patients With Type 2 Diabetes

MICHAEL JENSEN, MD
Designing a Comprehensive Weight Loss Program for Your Patients

THOMAS WADDEN, PhD
Effective Behavioral Modification Tools for Everyday Practice

LOUIS ARONNE, MD
The Role of Pharmacotherapy in a Comprehensive Weight Loss Program

Moderator
F. XAVIER PI-SUNYER, MD
Question and Answer/Discussion Session • Faculty Panel

F. XAVIER PI-SUNYER, MD
Concluding Remarks

Registration and Additional Information

To register by phone, call 1-888-499-3174 or fax your name, title, institution, and address to 212-645-6844. Please mention the key phrase "ADA."

Advanced registration is requested. On-site registration will be available, space permitting.

Continuing Medical Education Credit

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) by Postgraduate Institute for Medicine (PIM). PIM is accredited by the ACCME to provide continuing medical education for physicians.

PIM designates this continuing medical education activity for a maximum of two (2) credit hours in Category 1 of the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

This program is supported by an unrestricted educational grant from Roche Laboratories, Inc.

Introducing an innovation to help promote healing

For diabetic neuropathic foot ulcers...*

NEW REGRANEX® GEL 0.01%

(becaplermin)

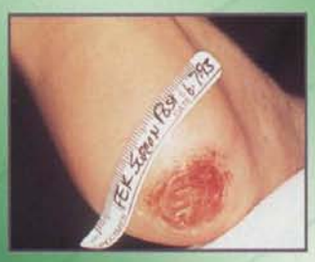
* REGRANEX Gel is indicated for diabetic neuropathic foot ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. REGRANEX Gel is an adjunct to, and not a substitute for, good wound care, which includes initial sharp debridement, pressure relief, and infection control.

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

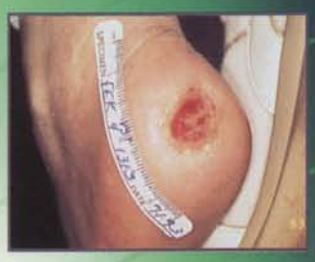
HELP PROMOTE HEALING

- 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

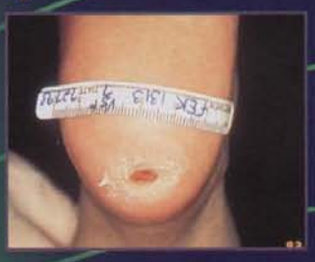
Case study results



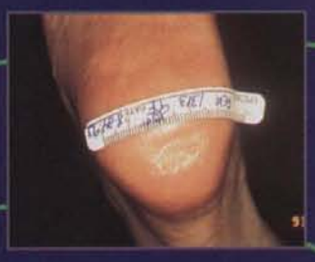
After debridement, prior to therapy with REGRANEX Gel



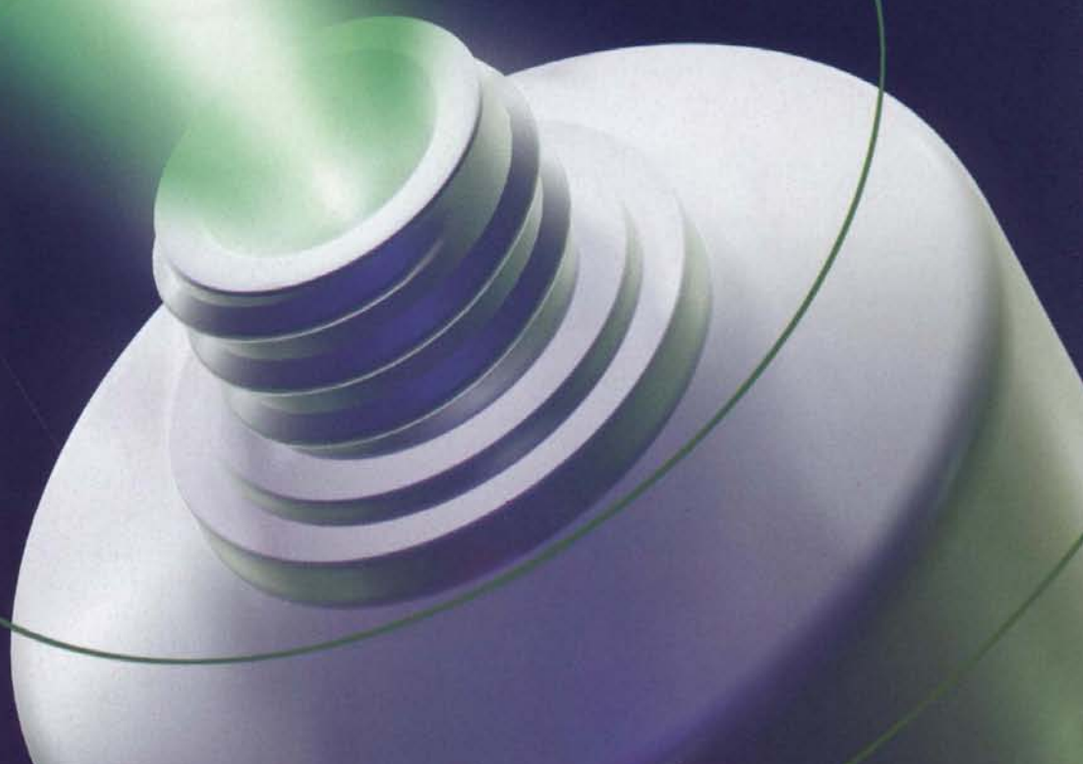
After 2 weeks of REGRANEX Gel plus good wound care



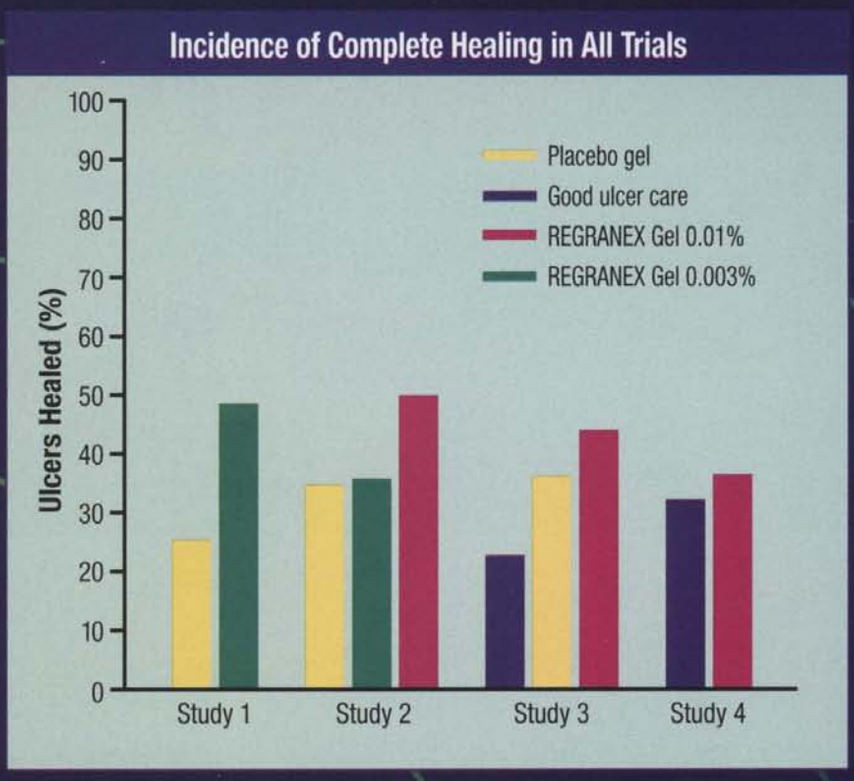
After 5 weeks of REGRANEX Gel plus good wound care



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

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ORTHO-McNEIL

TRANSFORMING WOUND CARE TO WOUND HEALING

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

 02J2881W 3/98

The first of a **NEW** drug class for type 2 diabetes

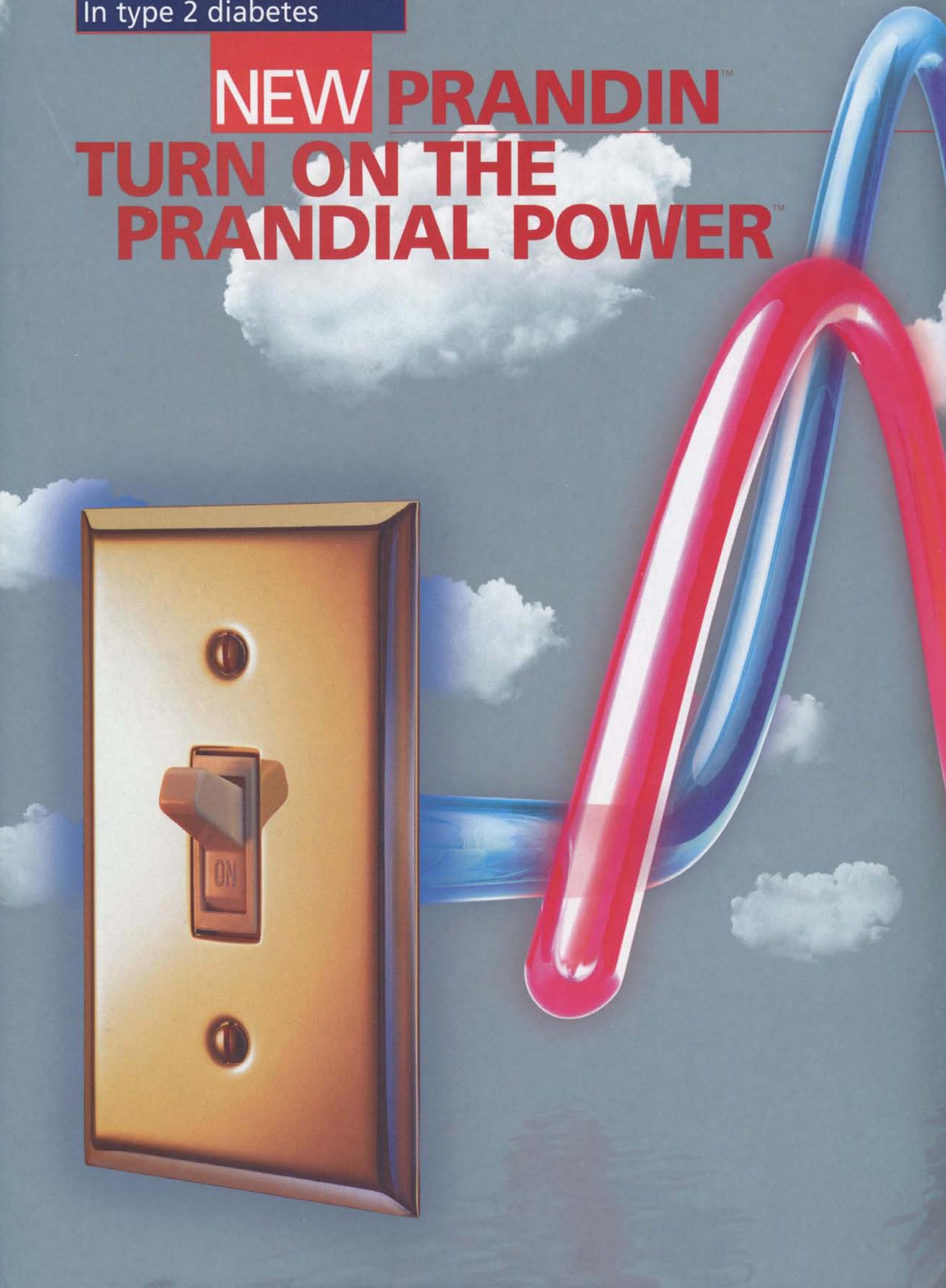
TURN ON THE PRANDIAL POWER™

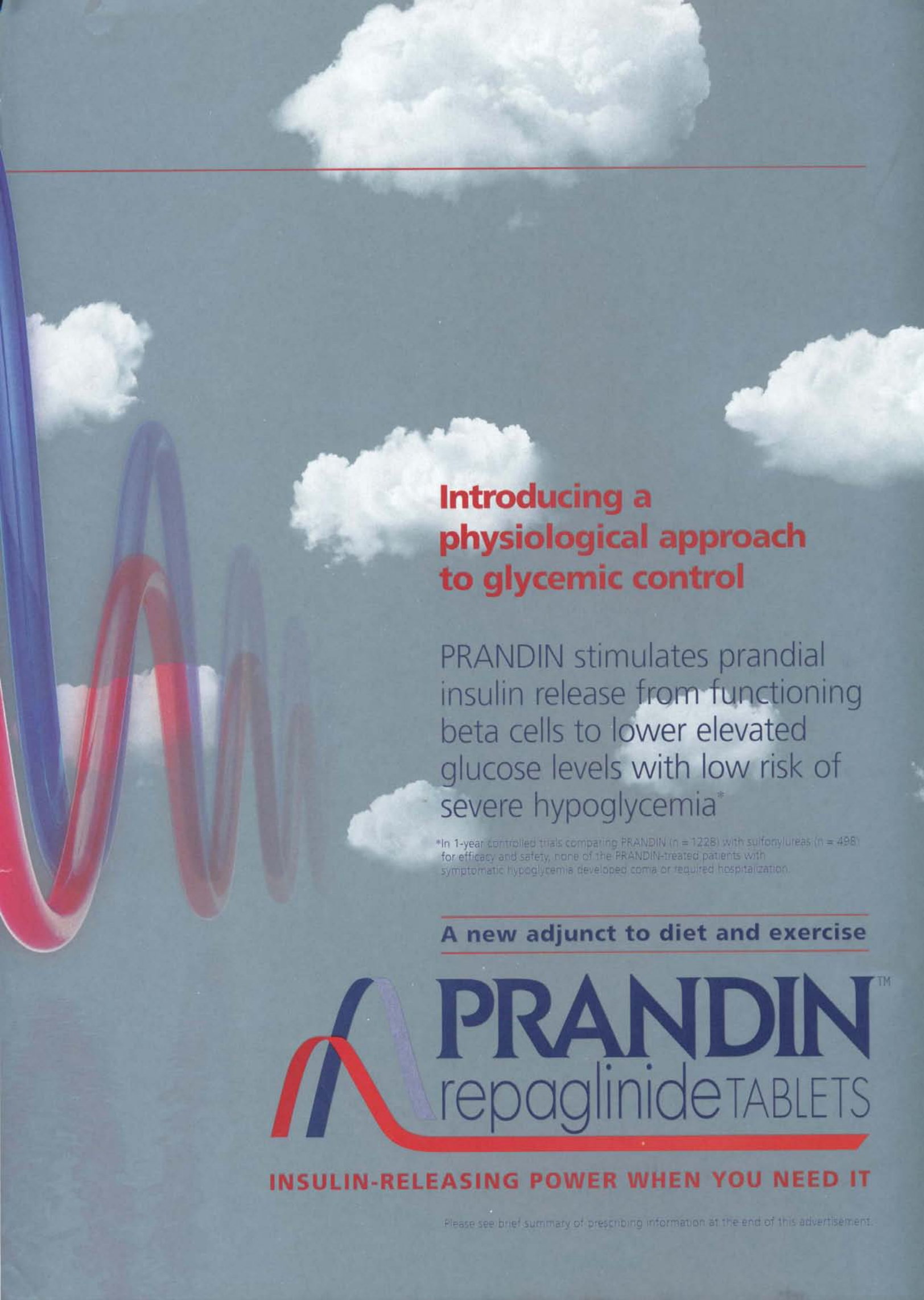
From Novo Nordisk, world leader in diabetes care

In type 2 diabetes

NEW PRANDIN™

TURN ON THE PRANDIAL POWER™





Introducing a physiological approach to glycemic control

PRANDIN stimulates prandial insulin release from functioning beta cells to lower elevated glucose levels with low risk of severe hypoglycemia*

*In 1-year controlled trials comparing PRANDIN (n = 1228) with sulfonylureas (n = 498) for efficacy and safety, none of the PRANDIN-treated patients with symptomatic hypoglycemia developed coma or required hospitalization.

A new adjunct to diet and exercise

PRANDIN™

repaglinide TABLETS

INSULIN-RELEASING POWER WHEN YOU NEED IT

Please see brief summary of prescribing information at the end of this advertisement.

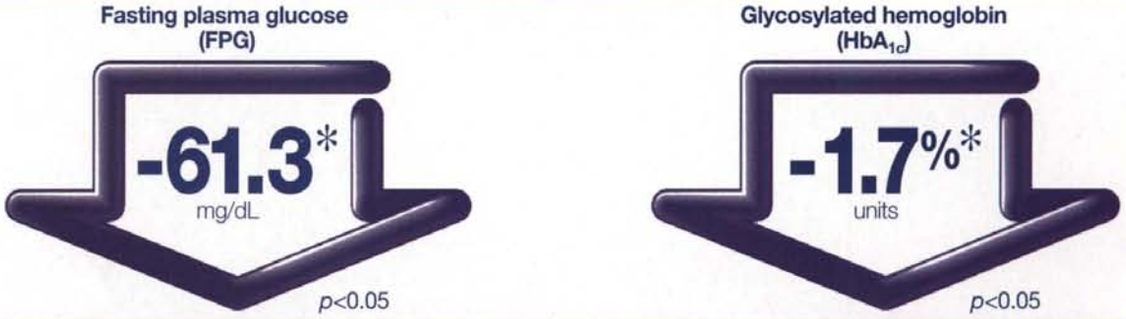
In type 2 diabetes

NEW PRANDIN™

TURN ON THE PRANDIAL POWER™

Effective first-line therapy

Significant reductions *vs* placebo in key parameters at 3 months

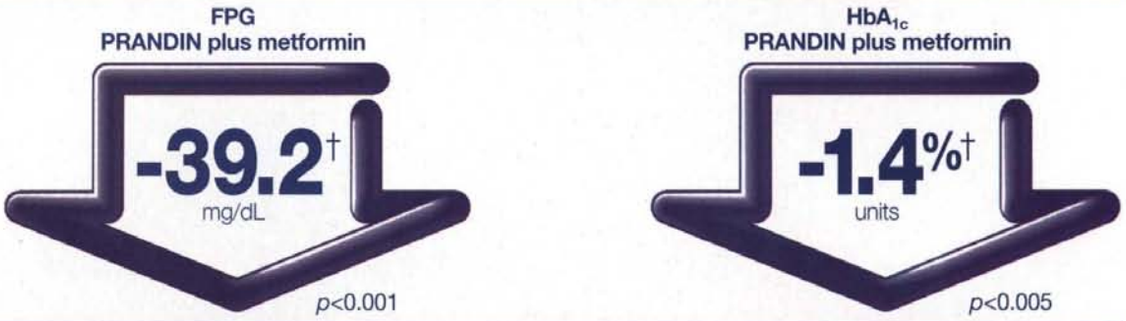


* Represents change between placebo and PRANDIN: FPG (placebo=30.3 mg/dL; PRANDIN=–31 mg/dL); HbA_{1c} (placebo=1.1% units; PRANDIN=–0.6% units).

A 3-month, double-blind, randomized, placebo-controlled, dose-titration study in patients with type 2 diabetes, with weekly increments of 0.25 mg, 0.5 mg, 1 mg, and 2 mg up to a maximum dose of 4 mg preprandially or until FPG <160 mg/dL was achieved (PRANDIN, n = 66; placebo, n = 33).

Synergistic with metformin

Significant reductions *vs* baseline in patients who previously failed on metformin alone[1]



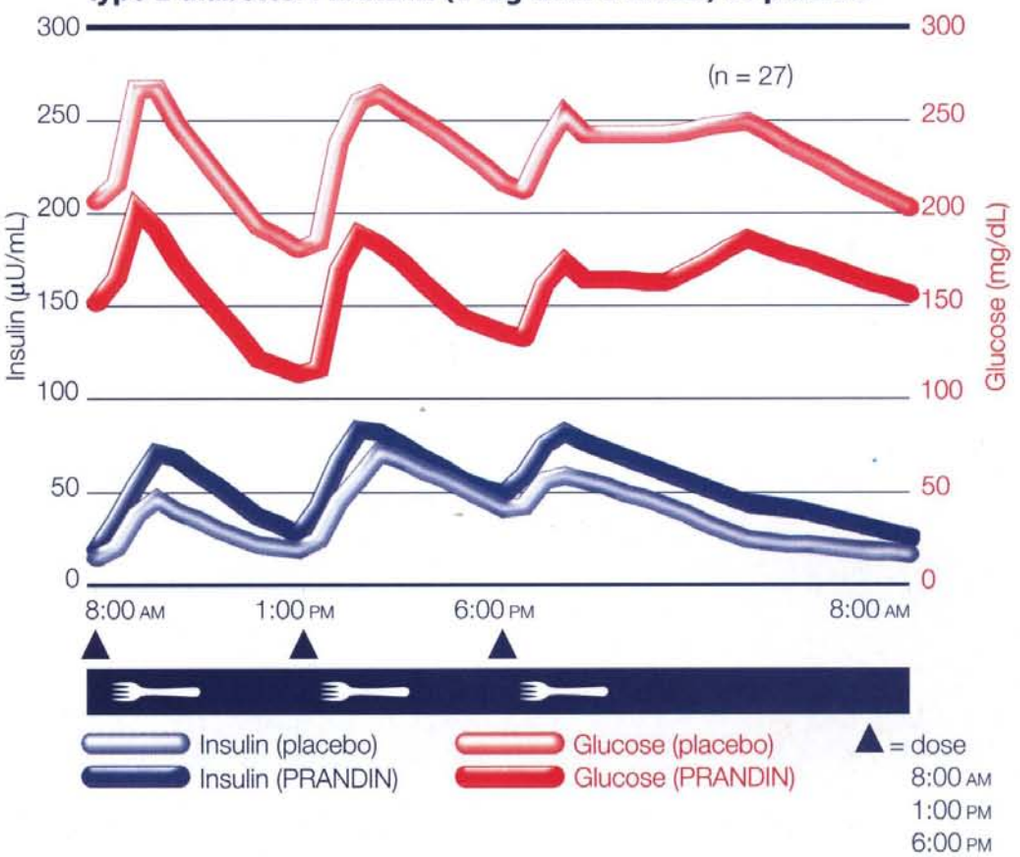
† Combination therapy change from baseline: metformin monotherapy: (FPG=–4.5 mg/dL; HbA_{1c}=–0.33% units); PRANDIN monotherapy: (FPG=8.8 mg/dL; HbA_{1c}=–0.38% units).

Results of a 3-month, multidose, double-blind, parallel-group, multicenter, 3-armed trial comparing metformin monotherapy (n = 27), PRANDIN monotherapy (n = 28), and the combination of metformin and PRANDIN (n = 27) in patients with type 2 diabetes not satisfactorily controlled on diet, exercise, and metformin monotherapy.[1]

Indicated in patients with type 2 diabetes uncontrolled by exercise, diet, and PRANDIN or metformin alone.

Glucose-lowering effect follows the prandial insulin surge[1]

Insulin and glucose response at steady state in patients with type 2 diabetes: PRANDIN (4 mg with 3 meals) *vs* placebo



A new adjunct to diet and exercise

PRANDIN™
repaglinide TABLETS

INSULIN-RELEASING POWER WHEN YOU NEED IT

Please see brief summary of prescribing information at the end of this advertisement.

In type 2 diabetes

NEW PRANDIN™ TURN ON THE PRANDIAL POWER™

A well defined metabolic profile

While hypoglycemia occurs with all oral hypoglycemic agents, results from clinical studies with PRANDIN document:

In active-controlled trials, hypoglycemia was reported in 16% of 1228 patients on PRANDIN and 20% of 498 patients on second-generation sulfonylureas (glyburide and glipizide). In placebo-controlled trials, hypoglycemia was reported by 31% of 352 patients on PRANDIN and 7% of 108 patients on placebo; 90 of the patients on PRANDIN who reported hypoglycemic symptoms (26% of the 352) were in a 6-month fixed-dose safety trial, which did not allow for dosage adjustments that might have averted hypoglycemia.

No hospitalizations or coma resulting from hypoglycemia in patients on PRANDIN therapy in 1-year controlled clinical trials.

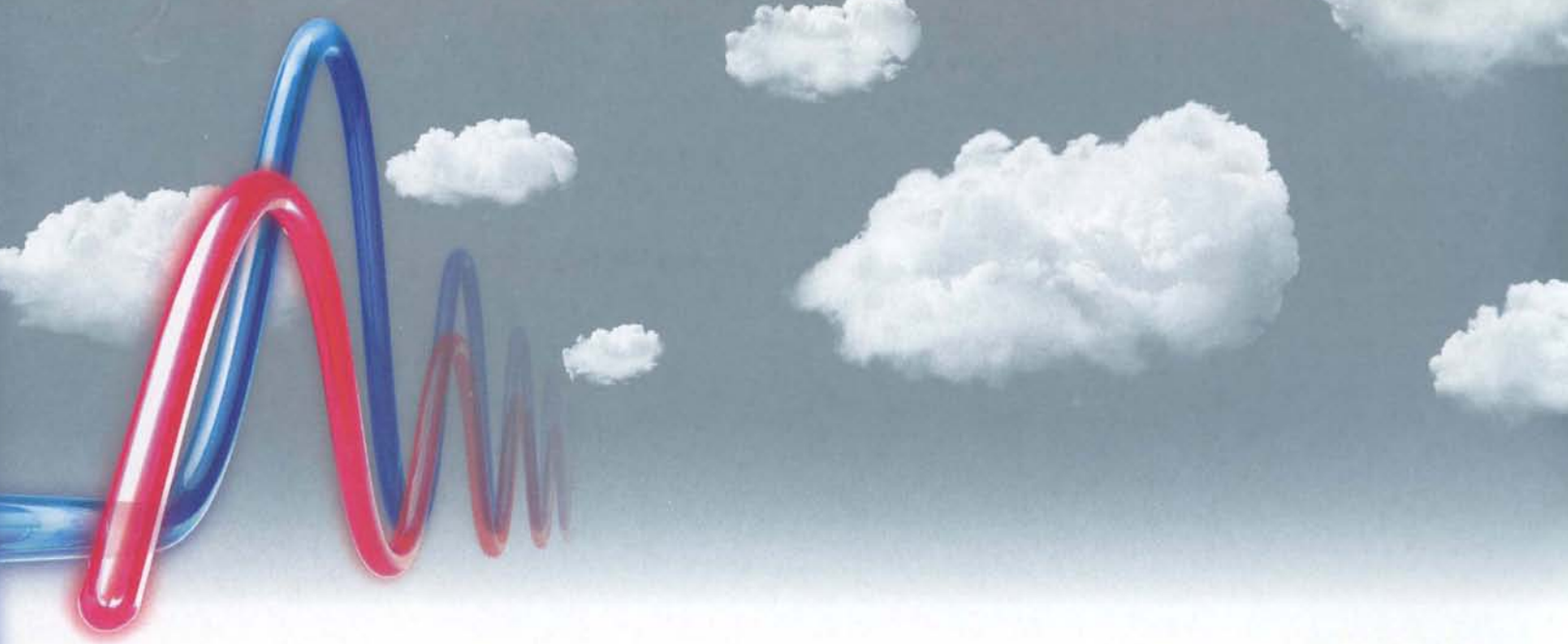
Low rate of discontinuation due to hypoglycemia

Placebo-controlled trials[1]		Long-term active-comparator trials[1]	
PRANDIN (n = 472)	Placebo (n = 131)	PRANDIN (n = 1228)	Sulfonylureas (n = 597)
0.6%	0%	1.4%	2.8%

The most common adverse events leading to discontinuation of PRANDIN therapy were hyperglycemia, hypoglycemia, and related symptoms.

Low risk of prolonged insulin stimulation

No weight gain in patients switched from sulfonylureas; weight gain averaged 3.3% in patients naive to pharmacologic therapy



Important safety information

Commonly reported adverse events (% of patients)*

	URI	Sinusitis	Rhinitis	Bronchitis	Nausea	Diarrhea	Constipation	Vomiting	Dyspepsia	Arthralgia	Back pain	Headache	Paresthesia	Chest pain	UTI	Tooth disorder	Allergy
Active-controlled trials																	
PRANDIN (n=1228)	10	3	7	6	3	4	2	2	4	3	6	9	2	2	3	<1	1
Sulfonylureas (n=498)	10	4	8	7	2	6	3	1	2	4	7	8	1	1	3	<1	<1
Placebo-controlled trials																	
PRANDIN (n=352)	16	6	3	2	5	5	3	3	2	6	5	11	3	3	2	2	2
Placebo (n=108)	8	2	3	1	5	2	2	3	2	3	4	10	3	1	1	0	0

*Events (excluding hypoglycemia) ≥ 2% for the PRANDIN group in the placebo-controlled studies and ≥ events in the placebo group.

GI disturbance rate similar to placebo

PRANDIN can be used in patients with impaired kidney function and should be used cautiously in patients with impaired liver function. (Please see CLINICAL PHARMACOLOGY, SPECIAL POPULATIONS section in brief prescribing information at the end of this advertisement.)

The individual incidence of cardiovascular events reported with PRANDIN in 1-year active-controlled trials was comparable to rates observed with other oral hypoglycemic agents (not greater than 1% except for chest pain [1.8%] and angina [1.8%]). The overall incidence of serious cardiovascular events was not significantly different for PRANDIN (4%) than for sulfonylureas (3%) in these trials. The UGDP study suggested increased cardiovascular risk with oral antidiabetic agents.[1]

A new adjunct to diet and exercise

PRANDIN™
repaglinide TABLETS

INSULIN-RELEASING POWER WHEN YOU NEED IT

Please see brief summary of prescribing information at the end of this advertisement.

In type 2 diabetes

NEW PRANDIN™ TURN ON THE PRANDIAL POWER™

"Don't start a meal without it"

PRANDIN should be taken preprandially (from 0 to 30 minutes before each meal)

Logical, meal-related dosing. Recommended dose range: 0.5 mg to 4 mg preprandially, up to 16 mg/day maximum.

Patients who miss a meal (or add an extra meal) should be instructed to omit (or add) the dose for that meal.

Starting dose for PRANDIN (alone or in combination with metformin)

Patient Profile	Dosage	Frequency
No previous treatment with blood glucose-lowering drugs, or HbA_{1c} <8%	0.5 mg	Preprandially, with each meal
Previous treatment with blood glucose-lowering drugs and HbA_{1c} ≥8%	1 or 2 mg	Preprandially, with each meal

PRANDIN was studied with preprandial doses at two, three, and four meals per day. The preprandial doses should be doubled, up to 4 mg, until satisfactory blood glucose response is achieved. At least 1 week should elapse to assess response after each dose adjustment.

A new adjunct to diet and exercise

PRANDIN™
repaglinide TABLETS

INSULIN-RELEASING POWER WHEN YOU NEED IT
Available in 0.5 mg, 1 mg, and 2 mg tablets

Please see brief summary of prescribing information at the end of this advertisement.

PRANDIN™ repaglinide TABLETS

PRANDIN™ (repaglinide tablets) 0.5 mg, 1 mg, and 2 mg

BRIEF SUMMARY: CONSULT PACKAGE INSERT BEFORE PRESCRIBING PRANDIN.

INDICATIONS AND USAGE PRANDIN is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with type 2 diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled satisfactorily by diet and exercise alone. PRANDIN is also indicated for use in combination with metformin to lower blood glucose in patients whose hyperglycemia cannot be controlled by exercise, diet, and either repaglinide or metformin alone.

CONTRAINDICATIONS PRANDIN is contraindicated in patients with diabetic ketoacidosis, with or without coma, in patients with type 1 diabetes, and in patients with known hypersensitivity to the drug or its inactive ingredients.

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.

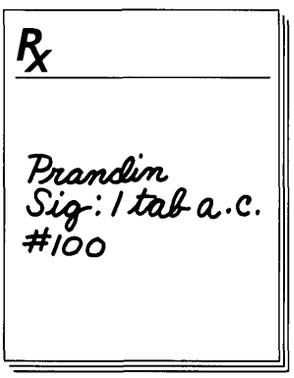
PRECAUTIONS Hypoglycemia: All oral blood glucose-lowering drugs are capable of producing hypoglycemia. Proper patient selection, dosage, and instructions to the patients are important to avoid hypoglycemic episodes. Hepatic insufficiency may cause elevated repaglinide blood levels and may diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemia. Elderly, 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 taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used. The frequency of hypoglycemia is greater in patients with type 2 diabetes who have not been previously treated with oral blood glucose-lowering drugs (naive) or whose HbA_{1C} is less than 8%. PRANDIN should be administered with meals to lessen the risk of hypoglycemia.

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 glycemic control may occur. At such times, it may be necessary to discontinue PRANDIN and administer insulin.

Renal insufficiency: Initial dosage adjustment does not appear to be necessary, but subsequent increases in PRANDIN should be made carefully in patients with type 2 diabetes who have renal function impairment or renal failure requiring hemodialysis.

Hepatic insufficiency: PRANDIN should be used cautiously in patients with impaired liver function. Longer intervals between dose adjustments should be utilized to allow full assessment of response.

Information for Patients: Patients should be informed of the potential risks and advantages of PRANDIN 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 and HbA_{1C}.The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development and concomitant administration of other glucose-lowering drugs should be explained to patients and responsible family members. Primary and secondary failure should also be explained. **Patients should be instructed to take PRANDIN before meals (2, 3, or 4 times a day preprandially).** Doses are usually taken within 15 minutes of the meal but time may vary from immediately preceding the meal to as long as 30 minutes before the meal. **Patients who skip a meal (or add an extra meal) should be instructed to skip (or add) a dose for that meal.**



Laboratory Tests: Response to PRANDIN should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels with a goal of decreasing these levels towards the normal range.

Drug Interactions: *In vitro* data indicate that repaglinide metabolism may be inhibited by antifungal agents like ketoconazole and miconazole, and antibacterial agents like erythromycin. Drugs that induce the cytochrome P-450 enzyme system 3A4 may increase repaglinide metabolism; such drugs include troglitazone, rifampicin, barbiturates, and carbamazepine. Drug interaction studies performed in healthy volunteers show that PRANDIN had no clinically relevant effect on the pharmacokinetic properties of digoxin, theophylline, or warfarin. Co-administration of cimetidine with PRANDIN did not significantly alter the absorption and disposition of repaglinide.The hypoglycemic action of oral blood glucose-lowering agents may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic 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.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term carcinogenicity studies were performed for 104 weeks at doses up to and including 120 mg/kg body weight/day (rats) and 500 mg/kg body weight/day (mice) or approximately 60 and 125 times clinical exposure, respectively, on a mg/m² basis. No evidence of carcinogenicity was found in mice or female rats. In male rats, there was an increased incidence of benign adenomas of the thyroid and liver. The relevance of these findings to humans is unclear. The no-effect doses for these observations in male rats were 30 mg/kg body weight/day for thyroid tumors and 60 mg/kg body weight/day for liver tumors, which are over 15 and 30 times, respectively, clinical exposure on a mg/m² basis. Repaglinide was non-genotoxic in a battery of *in vivo* and *in vitro* studies: Bacterial mutagenesis (Ames test), *in vitro* forward cell mutation assay in V79 cells (HGPRT), *in vitro* chromosomal aberration assay in human lymphocytes, unscheduled and replicating DNA synthesis in rat liver, and *in vivo* mouse and rat micronucleus tests. Fertility of male and female rats was unaffected by repaglinide administration at doses up to 80 mg/kg body weight/day (females) and 300 mg/kg body weight/day (males); over 40 times clinical exposure on a mg/m² basis.

Pregnancy: Pregnancy category C.

Teratogenic Effects: Safety in pregnant women has not been established. Repaglinide was not teratogenic in rats or rabbits at doses 40 times (rats) and approximately 0.8 times (rabbit) clinical exposure (on a mg/m² basis) throughout pregnancy. PRANDIN should be used during pregnancy only if it is clearly needed. Many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Offspring of rat dams exposed to repaglinide at 15 times clinical exposure on a mg/m² basis during days 17 to 22 of gestation and during lactation developed nonteratogenic skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. This effect was not seen at doses up to 2.5 times clinical exposure (on a mg/m² basis) on days 1 to 22 of pregnancy or at higher doses given during days 1 to 16 of pregnancy. Relevant human exposure has not occurred to date and therefore the safety of PRANDIN administration throughout pregnancy or lactation cannot be established.

Nursing Mothers: In rat reproduction studies, measurable levels of repaglinide were detected in the breast milk of the dams and lowered blood glucose levels were observed in the pups. Cross-fostering studies indicated that skeletal changes could be induced in control pups nursed by treated dams, although this occurred to a lesser degree than those pups treated *in utero*. Although it is not known whether repaglinide is excreted in human milk, some oral agents are known to be excreted by this route. A decision should be made as to whether PRANDIN should be discontinued in nursing mothers, or if mothers should discontinue nursing. If PRANDIN is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use: No studies have been performed in pediatric patients.

Geriatric Use: In repaglinide clinical studies of 24 weeks or greater duration, 415 patients were over 65 years of age. In one-year, active-controlled trials, no differences were seen in effectiveness or adverse events between these subjects and those less than 65 other than the expected age-related increase in cardiovascular events observed for PRANDIN and comparator drugs. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals to PRANDIN therapy cannot be ruled out.

ADVERSE REACTIONS In placebo-controlled trials, the adverse events reported in >2% of PRANDIN patients (n = 352) and with a greater frequency than in the placebo group (n = 108) and in active-controlled trials in PRANDIN patients (n = 1228) versus glyburide and glipizide patients (n = 498) were, respectively: hypoglycemia–31%, 7%, 16%, and 20%; URI–16%, 8%, 10%, and 10%; sinusitis–6%, 2%, 3%, and 4%; rhinitis–3%, 3%, 7%, and 8%; bronchitis–2%, 1%, 6%, and 7%; nausea–5%, 5%, 3%, and 2%; diarrhea–5%, 2%, 4%, and 6%; constipation–3%, 2%, 2%, and 3%; vomiting–3%, 3%, 2%, and 1%; dyspepsia–2%, 2%, 4%, and 2%; arthralgia–6%, 3%, 3%, and 4%; back pain–5%, 4%, 6%, and 7%; headache–11%, 10%, 9%, and 8%; paresthesia–3%, 3%, 2%, and 1%; chest pain–3%, 1%, 2%, and 1%; urinary tract infection–2%,1%, 3%, and 3%; tooth disorder–2%, 0%, <1%, and <1%; and allergy–2%, 0%, 1%, and <1%. Cardiovascular events also occur commonly in patients with type 2 diabetes. In one-year comparator trials, the incidence of individual events was not greater than 1% except for chest pain (1.8%) and angina (1.8%). The overall incidence of other cardiovascular events (hypertension, abnormal EKG, myocardial infarction, arrhythmias, and palpitations) was ≤1% and not different for PRANDIN and the comparator drugs. The incidence of serious cardiovascular adverse events added together, including ischemia, was slightly higher for repaglinide (4%) than for the sulfonylurea drugs glyburide and glipizide (3%) in controlled comparator clinical trials. Cardiac ischemic events occurred in 2% of patients in each treatment group, and deaths due to cardiovascular events in 0.1% of the PRANDIN group and 0.04% of the sulfonylurea group. PRANDIN treatment was not associated with excess mortality rates compared to rates observed with other oral hypoglycemic agent therapies.

Infrequent adverse events (<1% of patients): Less common adverse clinical or laboratory events observed in clinical trials included elevated liver enzymes, thrombocytopenia, leukopenia, and anaphylactoid reactions (one patient).

OVERDOSAGE In a clinical trial, patients received increasing doses of PRANDIN up to 80 mg a day for 14 days. There were few adverse effects other than those associated with the intended effect of lowering blood glucose. Hypoglycemia did not occur when meals were given with these high doses. 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 may continue until the physician is assured that the patient is out of danger. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery. There is no evidence that repaglinide is dialyzable using hemodialysis. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL.

More detailed information is available on request.

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

123612

March 1998

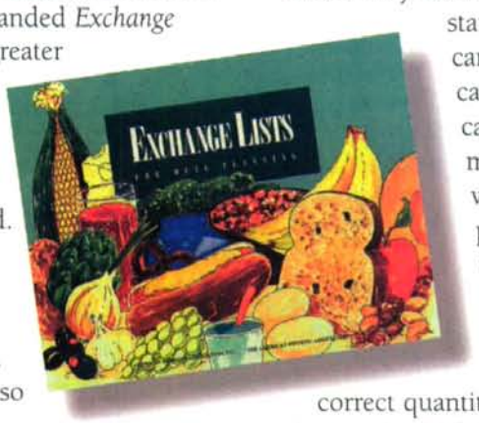
Novo Nordisk

Schering

New Tools Increase Meal Planning Flexibility

Exchange Lists for Meal Planning

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



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

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

	Nonmember	*Member*
Single copy #5601-02	*$1.50*	*$1.20*
Pkg of 25 #5601-01	*$37.50*	*$30.00*

Bulk Pricing (same for members and nonmembers)

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

The First Step in Diabetes Meal Planning

Also developed jointly by the American Diabetes Association and the American Dietetic Association, this colorful tri-fold brochure provides your patients with basic diabetes nutrition guidelines. It opens to an 11" x 18" poster depicting a diabetes food guide pyramid. Written on a very basic level for easy comprehension, this informative pamphlet is ideal for newly diagnosed patients, especially if they are not able to meet with a dietitian right away. Sold in packages of 25. #5605-01

Nonmember: $9.00; Member: $7.20

To order, call 1-800/232-6733 or fax your order to: 770/442-9742

What's new with the Exchange Lists?

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

Visit our bookstore on the internet @ http://www.merchant.diabetes.org

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

Item #	Item Name	Qty	Unit Price	Total

Shipping & Handling

up to $25.00	add $4.99
$25.01–$60.00	add $5.99
over $60.00	add 10%

Publications Subtotal ..... $_____
VA Residents add 4.5% tax ..... $_____
GA Residents add 7% tax ..... $_____
Shipping & Handling (see chart) $_____
Total Due ..... $_____

Allow 2-3 weeks for shipment. Add $4.99 for each additional shipping address. Add $15 for each address outside the U.S. Foreign orders must be paid in US funds, drawn on a US bank.

Ship To

First Name _____ Middle Initial _____ Last Name _____

Address _____

City/State/Zip _____

Phone _____ Member # _____ P26C0598

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

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

American Diabetes Association.

WHEN THE RELATIONSHIP SUFFERS FROM ERECTILE DYSFUNCTION

NOW THERE'S E D

The EDEX patient kit contains everything needed for self-injection:

- Single-dose vial of lyophilized powder
- Prefilled syringe with sterile diluent and plunger rod
- Two ½-inch needles: 27G and 30G
- Two alcohol swabs
- Detailed patient instructions

*EDEX is not a cure for erectile dysfunction. The underlying treatable medical causes should be diagnosed and treated prior to initiation of therapy. The therapeutic effect of each dose is temporary. If priapism occurs, the patient should seek immediate medical attention. EDEX should be used no more than 3 times per week with at least 24 hours between each dose.

EDEX is contraindicated in men with known hypersensitivity to alprostadil or other prostaglandins, men with conditions that might predispose them to priapism, and patients with penile implants or anatomical deformities of the penis. EDEX should not be used in men for whom sexual activity is inadvisable or contraindicated.

The injection of EDEX can induce a small amount of bleeding at the site of injection. Patients should be counseled about the protective measures that are necessary to guard against sexually transmitted or blood-borne diseases.

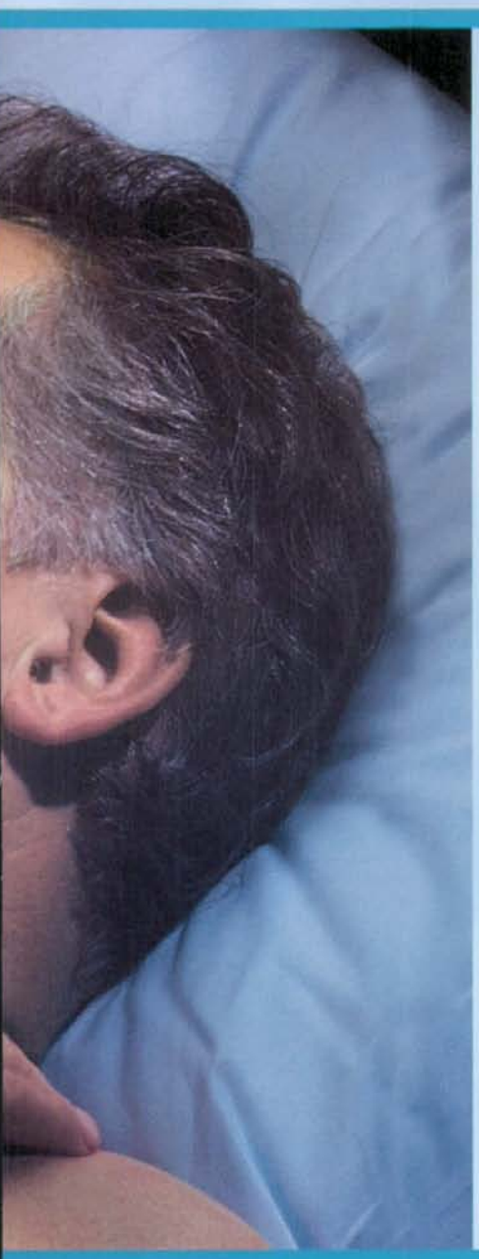
†588 of 894 patients had an optimum dose determined during the titration period. Patients received in-office evaluations, dose titration, and proper training techniques prior to the open-label, at-home extension period, which ranged from 6 to 12 months.

‡Based on direct cost per microgram for the at-home patient pack: EDEX, 5 mcg, $1.99; 10 mcg, $1.32; 20 mcg, $0.85; 40 mcg, $0.62. Caverject, 5 mcg, $2.17; 10 mcg, $1.45; 20 mcg, $0.93; 40 mcg, N/A. Price comparison does not imply comparable safety or efficacy. Prices may not reflect actual prices paid by patients or pharmacies.

Caverject® (alprostadil for injection) is a registered trademark of Pharmacia & Upjohn.

Please see brief summary of prescribing information.

E X™ (ALPROSTADIL FOR INJECTION)



Effectively restores erectile function...

Impressive at-home efficacy rates in clinical trials, 539 patients who self-injected EDEX at home had a mean rate of response, with an erection sufficient for intercourse, of 85% to 89%.[†1]

Confidently restores erectile function...

Established safety profile in clinical trials involving 1,065 patients with erectile dysfunction. The most common side effect experienced by patients was penile pain, reported by 31% of EDEX patients vs 9% of placebo patients in placebo-controlled studies. Patients judged the intensity of painful injections as mild (80%), moderate (16%), or severe (4%). Patient reports of penile pain decreased over time.

...with important benefits for you and your patients

Four dosage strengths (5, 10, 20, 40 mcg).
Simplifies the titration process and allows for economical dosing.

Priced lower than Caverject.®
Microgram per microgram, EDEX is less expensive than Caverject,® providing your patients an effective, yet more affordable treatment option.[‡1,2]

Refrigeration is not necessary.
Room temperature storage is convenient for both you and your patients.

Two injection choices.
Patients can choose a 27G or the thinner 30G sterile needle.

Complete patient support.
Comprehensive education and support for your patients with valuable tools for your office.

E D E X™

(ALPROSTADIL FOR INJECTION)

STERILE POWDER

RESTORE ERECTILE FUNCTION*

Detailed EDEX product information is available through your Schwarz Pharma representative and through our Internet web site: **www.edex.com**

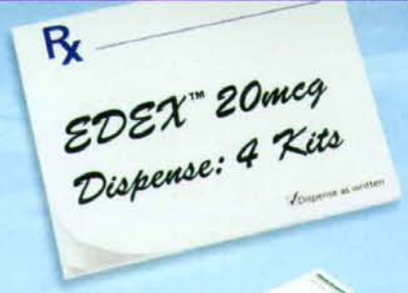
NOW THERE'S

EDEX™

(ALPROSTADIL FOR INJECTION)

STERILE POWDER

RESTORE ERECTILE FUNCTION*



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EDEX™

(alprostadil for injection)
For Intracavernous Use Only
Sterile Powder

The following is a Brief Summary. For complete prescribing information, see package insert.

INDICATIONS AND USAGE: Treatment of erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed etiology.

CONTRAINDICATIONS: Known hypersensitivity to alprostadil or other prostaglandins; conditions that might predispose the patient to priapism, such as sickle cell anemia or trait, multiple myeloma, or leukemia; anatomical penile deformity, such as angulation, cavernosal fibrosis, or Peyronie's disease; **and penile implants.** EDEX should not be used in men for whom sexual activity is inadvisable or contraindicated. Do not use EDEX in women, children, or newborns.

WARNINGS: Prolonged erections >4 hours occurred in 4% of patients treated up to 24 months. Incidence of priapism (erections >6 hours) was <1% with use for up to 24 months. In most cases, spontaneous detumescence occurred. Pharmacologic intervention and/or aspiration of blood from the corpora was necessary in 1.6% of 311 patients with prolonged erections/priapism. Titrate EDEX slowly to the lowest effective dose to minimize the chance of prolonged erection or priapism. Instruct the patient to immediately report and seek medical assistance for any erection that persists longer than 6 hours. Failure to treat priapism immediately may result in penile tissue damage and permanent loss of potency.

PRECAUTIONS: *General:* 1) EDEX can lead to increased peripheral blood levels of PGE_1 and its metabolites, especially in patients with significant corpora cavernosa venous leakage; hypotension and/or dizziness may occur. 2) Use regular patient follow-up, with careful examination of the penis at the start of therapy and at regular intervals (e.g. 3 months), to identify any penile changes. Penile fibrosis, including Peyronie's disease, was reported in 7.8% of patients in clinical studies up to 24 months. Stop treatment with EDEX in patients who develop penile angulation, cavernosal fibrosis, or Peyronie's disease. Treatment can be resumed if the penile abnormality subsides. 3) EDEX combined with other vasoactive agents was not systematically studied; the use of such combinations is not recommended. 4) After EDEX injection, compress the injection site for five minutes or until bleeding stops. Anticoagulant therapy, such as warfarin or heparin, may increase the tendency for bleeding after injection. 5) Diagnose and treat underlying treatable medical causes of erectile dysfunction before starting therapy with EDEX. 6) Instruct the patient not to re-use or share needles or syringes and not to let anyone else use his prescription medicines. 7) *Drug Interactions:* Exercise caution with concomitant administration of heparin and EDEX. *Information for Patients:* Thorough training in self-injection technique is required before EDEX can be used at home. The dose is established in the physician's office. Carefully follow preparation instructions included with EDEX. Discard vials with precipitates or discoloration. If dosage prescribed is <1 mL, the entire amount of solution will not need to be withdrawn to reach the prescribed dose. Properly discard needles after use; do not re-use or share with others. Use solution immediately after reconstitution. Follow the instructions in the patient information pamphlet. The vial is designed for single use; therefore, discard the vial and any remaining solution once the proper amount is withdrawn. Do not change the prescribed dose without physician consultation. EDEX should produce an erection in 5 to 20 minutes. Do not exceed an injection frequency of 3 times per week; separate each use by at least 24 hours. Patients should know the possible side effects of EDEX and what to do if side effects occur. Patients must return for regular checkups for treatment benefit and safety assessments. Counsel patients about protective measures necessary to guard against the spread of sexually transmitted diseases, including the human immunodeficiency virus (HIV). The small amount of injection-site bleeding that can occur in some patients could increase the risk of transmitting blood-borne diseases between partners. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* Long-term carcinogenicity studies have not been conducted. Alprostadil was not mutagenic in a variety of assays. Alprostadil did not cause any adverse effects on fertility or general reproductive performance when administered intraperitoneally to male or female rats. *Pregnancy, Nursing Mothers and Pediatric Use:* EDEX is not indicated for use in women or pediatric patients. *Geriatric Use:* In clinical studies, geriatric patients required, on average, higher minimally effective doses and had a higher rate of lack of effect (optimum dose not determined). Overall differences in safety were not observed between geriatric patients and younger patients. Geriatric patients should be dosed and titrated according to the same DOSAGE AND ADMINISTRATION recommendations as younger patients, and the lowest possible effective dose should always be used.

ADVERSE REACTIONS: EDEX, administered in doses ranging from 1 to 40 mcg per injection for periods up to 24 months, has been evaluated for safety in over 1,065 patients with erectile dysfunction. Discontinuation of therapy due to a side effect in clinical trials was required in approximately 9% of patients treated with EDEX and in <1% of patients treated with placebo. *Local Adverse Reactions:* The following local adverse reactions were reported in studies including 1,065 patients treated with EDEX for up to two years. *Penile Pain:* Penile pain was mild in intensity for 80% of painful injections, moderate in intensity for 16% of painful injections, and severe in intensity for 4% of painful injections. The frequency of penile pain reports decreased over time; forty-one percent of the patients experienced pain during the first 2 months and 3% of the patients experienced pain during months 21-24. *Prolonged Erection/Priapism:* See WARNINGS. *Hematoma/Ecchymosis:* Most cases of hematoma and ecchymosis were attributed to faulty injection technique. Local reactions reported in ≥1% of patients treated during all study periods with EDEX (N=1,065): penile pain during injection (29%); penile pain during erection (35%); penile pain after erection (30%); penile pain-other (11%); prolonged erection >4 ≤6 hours (4%); prolonged erection >6 hours (<1%); bleeding (15%); hematoma (5%); ecchymosis (4%); penile angulation (7%); penile fibrosis (5%); cavernous body fibrosis (2%); Peyronie's disease (1%); faulty injection technique (6%); penis disorder (3%); erythema (2%). *Systemic Adverse Experiences:* Reported in controlled and uncontrolled studies in ≥1% of patients treated for up to 24 months with EDEX (N=1,065): upper respiratory tract infection (5%); influenza-like symptoms (3%); headache (2%); infection (2%); pain (2%); back pain (2%); hypertension (2%); hypertriglyceridemia (2%); myocardial infarction (1%); abnormal ECG (1%); hypercholesterolemia (1%); hyperglycemia (1%); prostate disorder (1%); testicular pain (1%); inguinal hernia (1%); skin disorder (1%); abnormal vision (1%); leg pain (1%); and sinusitis (1%). Hemodynamic changes were observed during clinical studies but did not appear to be dose-dependent. Four patients (<1%) reported clinical symptoms of hypotension such as dizziness or syncope. EDEX had no clinically important effect on serum or urine laboratory tests.

DOSAGE AND ADMINISTRATION: *EDEX in the Treatment of Erectile Dysfunction:* The dosage range is 1 to 40 mcg given as an intracavernous injection over a 5 to 10 second interval. Doses greater than 40 mcg have not been studied. A ½ inch, 27 or 30 gauge needle is generally recommended. The patient should not exceed the optimum EDEX dose which was determined in the doctor's office. Use the lowest possible effective dose. *Initial Titration in Physicians Office:* Follow the initial titration instructions that appear in the product package insert. Dosage titration instructions differ depending on erectile dysfunction etiology. *At-Home (Maintenance Therapy) Dosing Instructions:* Properly instruct and train the patient in the self-injection technique, and instruct the patient on the appropriate needles to use for reconstitution and injection. Instruct the patient to discard any needles which become bent as these needles may break. Carefully assess the patient's skills and competence with this procedure. The dose selected for self-injection therapy should provide an erection that is satisfactory for sexual activity and is maintained for no longer than 1 hour. Reduce the dose if the erection lasts longer than 1 hour. Use the lowest effective dose. Initiate self-injection therapy at home with the dose that was determined in the physician's office. Dose adjustment may be required and should be made only after consultation with the physician. Exercise careful and continuous follow-up of patients on self-injection therapy especially for initial self-injections. Recommended injection frequency is no more than 3 times weekly, with at least 24 hours between uses. Instruct the patient in the proper disposal of the syringe, needles, and single-use vial. See the patient every 3 months during self-injection therapy to assess treatment and, if needed, to adjust the dose. Instruct the patient to follow the enclosed patient information pamphlet. **Preparation of Solution:** Refer to product package insert for reconstitution instructions. **Stability:** Refer to product package insert for stability information.

CAUTION: Federal law prohibits dispensing without prescription.

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Milwaukee, WI 53201

By Abbott Laboratories
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References:
1. Data on file; Schwarz Pharma, Inc.
2. *Red Book Update,* June 1997.

SCHWARZ PHARMA

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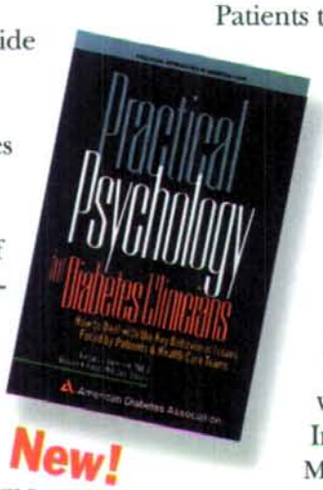

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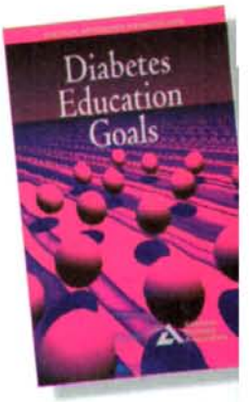

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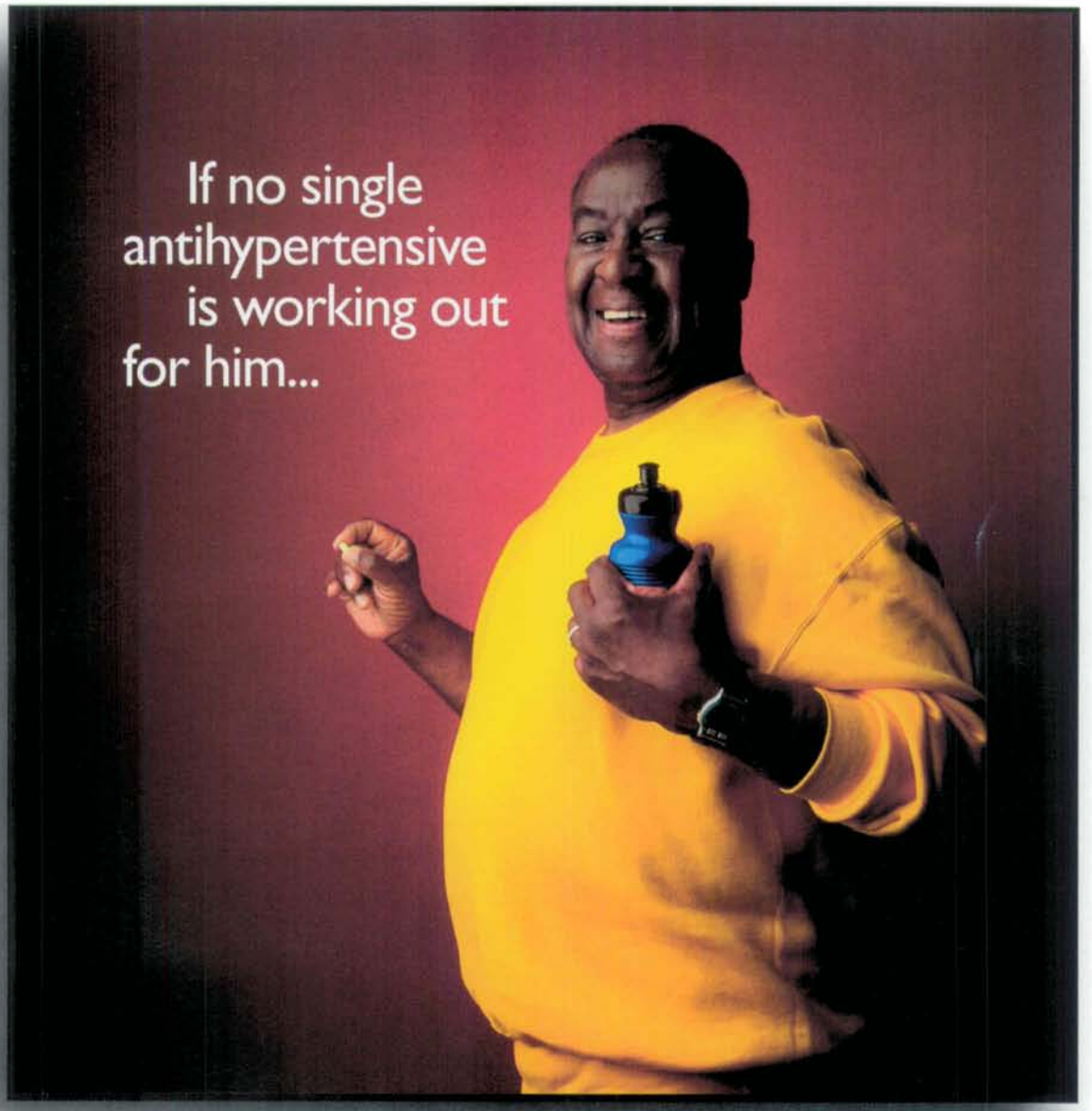

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Also, Cardura is well tolerated. The side effects reported significantly more often than placebo in hypertension studies were dizziness, somnolence, and fatigue. These were generally mild and transient. Only 2% of patients discontinued therapy due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

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Please see brief summary of prescribing information on adjacent page.

TAKES THE PRESSURE OFF

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References: 1. Neaton JD, Grimm RH Jr, Prineas RJ, et al, for the Treatment of Mild Hypertension Study Research Group. Treatment of Mild Hypertension Study: final results. *JAMA*. 1993;270:713-724. **2**. Brown MJ, Dickerson JEC. Synergism between alpha$_1$-blockade and angiotensin converting enzyme inhibition in essential hypertension. *J Hypertens*. 1991;9(suppl 6):S362-S363. **3**. Soltero I, Guevara J, Silva H, Velasco M. A multicenter study of doxazosin in the treatment of severe essential hypertension. *Am Heart J*. 1988;116:1767-1771. **4**. Brown MJ, Dickerson JEC. Alpha-adrenoceptor blockade and Ca^{++} blockade: a new combination for the treatment of hypertension. *Br J Clin Pharmacol*. 1994;37:474P. **5**. Ferrara LA, Di Marino L, Russo O, Marotta T, Mancini M, on behalf of the DoCHH Study Group. Doxazosin and captopril in mildly hypercholesterolemic hypertensive patients: the Doxazosin-Captopril in Hypercholesterolemic Hypertensives Study. *Hypertension*. 1993;21:97-104. **6**. Lehtonen A, the Finnish Multicenter Study Group. Lowered levels of serum insulin, glucose, and cholesterol in hypertensive patients during treatment with doxazosin. *Current Therapeutic Research*. 1990;47:278-284.

CARDURA® (doxazosin mesylate) Tablets

Brief Summary

CONTRAINDICATIONS

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

WARNINGS

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

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur, during both the day and night.

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

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

In placebo-controlled, clinical trials in BPH, 3 out of 665 patients (0.5%) taking doxazosin reported syncope. Two of the patients were taking 1 mg doxazosin, while one patient was taking 2 mg doxazosin when syncope occurred. In the open-label, long-term extension follow-up of approximately 450 BPH patients, there were 3 reports of syncope (0.7%). One patient was taking 2 mg, one patient was taking 8 mg and one patient was taking 12 mg when syncope occurred. In a clinical pharmacology study, one subject receiving 2 mg experienced syncope.

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

Priapism: Rarely (probably less frequently than one in every several thousand patients), alpha$_1$ antagonists such as doxazosin have been associated with priapism (painful penile erection, sustained for hours and unrelieved by sexual intercourse or masturbation). Because this condition can lead to permanent impotence if not promptly treated, patients must be advised about the seriousness of the condition (see **PRECAUTIONS: Information for Patients**).

PRECAUTIONS

General:

Prostate Cancer: Carcinoma of the prostate causes many of the symptoms associated with BPH and the two disorders frequently co-exist. Carcinoma of the prostate should therefore be ruled out prior to commencing therapy with CARDURA©.

Orthostatic Hypotension: While syncope is the most severe orthostatic effect of CARDURA©, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo can occur, especially at initiation of therapy or at the time of dose increases.

a) Hypertension

These symptoms were common in clinical trials in hypertension, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

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

b) Benign Prostatic Hyperplasia

In placebo-controlled trials in BPH, the incidence of orthostatic hypotension with doxazosin was 0.3% and did not increase with increasing dosage (to 8 mg/day). The incidence of discontinuations due to hypotensive or orthostatic symptoms was 3.3% with doxazosin and 1% with placebo. The titration interval in these studies was one to two weeks.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution. As alpha-antagonists can cause orthostatic effects, it is important to evaluate standing blood pressure two minutes after standing and patients should be advised to exercise care when arising from a supine or sitting position.

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

Information for Patients (See Patient Package Insert): Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with CARDURA© or any selective alpha$_1$ adrenoceptor antagonist, requiring caution in people who must drive or operate heavy machinery.

Patients should be advised about the possibility of priapism as a result of treatment with alpha$_1$ antagonists. Patients should know that this adverse event is very rare. If they experience priapism, it should be brought to immediate medical attention for if not treated promptly it can lead to permanent erectile dysfunction (impotence).

Drug/Laboratory Test Interactions: CARDURA© does not affect the plasma concentration of prostate specific antigen in patients treated for up to 3 years. Both doxazosin, an alpha$_1$ inhibitor, and finasteride, a 5-alpha reductase inhibitor, are highly protein bound and hepatically metabolized. There is no definitive controlled clinical experience on the concomitant use of alpha$_1$ inhibitors and 5-alpha reductase inhibitors at this time.

Impaired Liver Function: CARDURA© (doxazosin mesylate) should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACOLOGY).

Leukopenia/Neutropenia: Analysis of hematologic data from hypertensive patients receiving CARDURA© in controlled hypertension clinical trials showed that the mean WBC (N = 474) and mean neutrophil counts (N = 419) were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. In BPH patients the incidence of clinically significant WBC abnormalities was 0.4% (2/459) with CARDURA© and 0% (0/147) with placebo, with no statistically significant difference between the two treatment groups. A search through a data base of 2400 hypertensive patients and 665 BPH patients revealed 4 hypertensives in which drug-related neutropenia could not be ruled out and one BPH patient in which drug related leukopenia could not be ruled out. Two hypertensives had a single low value on the last day of treatment. Two hypertensives had stable, non-progressive neutrophil counts in the 1000/mm^3 range over periods of 20 and 40 weeks. One BPH patient had a decrease from WBC count of 4800/mm^3 to 2700/mm^3 at the end of the study; there was no evidence of clinical impairment. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA©. No patients became symptomatic as a result of the low WBC or neutrophil counts.

Drug Interactions: Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that CARDURA© has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA© has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta-blocking agents, and nonsteroidal anti-inflammatory drugs. In a placebo-controlled trial in normal volunteers, the administration of a single 1 mg dose of doxazosin on day 1 of a four-day regimen of oral cimetidine (400 mg twice daily) resulted in a 10% increase in mean AUC of doxazosin (p=0.006), and a slight but not statistically significant increase in mean C_{max} and mean half-life of doxazosin. The clinical significance of this increase in doxazosin AUC is unknown.

In clinical trials, CARDURA© tablets have been administered to patients on a variety of concomitant medications; while no formal interaction studies have been conducted, no interactions were observed. CARDURA© tablets have been used with the following drugs or drug classes: 1) analgesic/anti-inflammatory (e.g., acetaminophen, aspirin, codeine and codeine combinations, ibuprofen, indomethacin); 2) antibiotics (e.g., erythromycin, trimethoprim and sulfamethoxazole, amoxicillin); 3) antihistamines (e.g., chlorpheniramine); 4) cardiovascular agents (e.g., atenolol, hydrochlorothiazide, propranolol); 5) corticosteroids; 6) gastrointestinal agents (e.g., antacids); 7) hypoglycemics and endocrine drugs; 8) sedatives and tranquilizers (e.g., diazepam); 9) cold and flu remedies.

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

ADVERSE REACTIONS

A. *Benign Prostatic Hyperplasia*

The incidence of adverse events has been ascertained from worldwide clinical trials in 965 BPH patients. The incidence rates presented below (Table 3) are based on combined data from seven placebo-controlled trials involving once daily administration of CARDURA© in doses of 1-16 mg in hypertensives and 0.5-8 mg in normotensives. The adverse events when the incidence in the CARDURA© group was at least 1% are summarized in Table 3. No significant difference in the incidence of adverse events compared to placebo was seen except for dizziness, fatigue, hypotension, edema and dyspnea. Dizziness and dyspnea appeared to be dose-related.

In BPH, adverse reactions during placebo-controlled studies of CARDURA© (N=665) vs placebo (N=300), respectively, were: back pain (1.8% vs 2.0%), chest pain (1.2% vs 0.7%), fatigue (8.0%* vs 1.7%), headache (9.9% vs 9.0%), influenza-like symptoms (1.1% vs 1.0%), pain (2.0% vs 1.0%), hypotension (1.7%* vs 0.0%), palpitation (1.2% vs 0.3%), abdominal pain (2.4% vs 2.0%), diarrhea (2.3% vs 2.0%), dyspepsia (1.7% vs 1.7%), nausea (1.5% vs 0.7%), edema (2.7%* vs 0.7%), dizziness/vertigo (15.6%* vs 9.0%), mouth dry (1.4% vs 0.3%), somnolence (3.0% vs 1.0%), dyspnea (2.6%* vs 0.3%), respiratory disorder (1.1% vs 0.7%), vision abnormal (1.4% vs 0.7%), impotence (1.1% vs 1.0%), urinary tract infection (1.4% vs 2.3%), sweating increased (1.1% vs 1.0%), anxiety (1.1% vs 0.3%), insomnia (1.2% vs 0.3%). *$p \leq 0.05$ for treatment differences

In these placebo-controlled studies of 665 CARDURA© (doxazosin mesylate) patients, treated for a mean of 85 days, additional adverse reactions have been reported. These are less than 1% and not distinguishable from those that occurred in the placebo group. Adverse reactions with an incidence of less than 1% but of clinical interest are (CARDURA© vs. placebo): *Cardiovascular System:* angina pectoris (0.6% vs. 0.7%), postural hypotension (0.3% vs. 0.3%), syncope (0.5% vs. 0.0%), tachycardia (0.9% vs. 0.0%); *Urogenital System:* dysuria (0.5% vs. 1.3%), and *Psychiatric Disorders:* libido decreased (0.8% vs. 0.3%). The safety profile in patients treated for up to three years was similar to that in the placebo-controlled studies.

The majority of adverse experiences with CARDURA© were mild.

B. *Hypertension*

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

In controlled hypertension clinical trials directly comparing CARDURA© to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue/malaise. Postural effects and edema appeared to be dose related. The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. Table 4 summarizes those adverse experiences (possibly/probably related) reported for patients in these hypertension studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

In hypertension, adverse reactions during placebo-controlled studies of CARDURA© (N=339) vs placebo (N=336), respectively, were: dizziness (19% vs 9%), vertigo (2% vs 1%), postural hypotension (0.3% vs 0%), edema (4% vs 3%), palpitation (2% vs 3%), arrhythmia (1% vs 0%), hypotension (1% vs 0%), tachycardia (0.3% vs 1%), peripheral ischemia (0.3% vs 0%), rash (1% vs 1%), pruritus (1% vs 1%), arthralgia/arthritis (1% vs 0%), muscle weakness (1% vs 0%), myalgia (1% vs 0%), headache (14% vs 16%), paresthesia (1% vs 1%), kinetic disorders (1% vs 0%), ataxia (1% vs 0%), hypertonia (1% vs 0%), muscle cramps (1% vs 0%), mouth dry (2% vs 2%), flushing (1% vs 0%), vision abnormal (2% vs 1%), conjunctivitis/eye pain (1% vs 1%), tinnitus (1% vs 0.3%), somnolence (5% vs 1%), nervousness (2% vs 2%), depression (1% vs 1%), insomnia (1% vs 1%), sexual dysfunction (2% vs 1%), nausea (3% vs 4%), diarrhea (2% vs 3%), constipation (1% vs 1%), dyspepsia (1% vs 1%), flatulence (1% vs 1%), abdominal pain (0% vs 2%), vomiting (0% vs 1%), rhinitis (3% vs 1%), dyspnea (1% vs 1%), epistaxis (1% vs 0%), polyuria (2% vs 0%), urinary incontinence (1% vs 0%), micturition frequency (0% vs 2%), fatigue/malaise (12% vs 6%), chest pain (2% vs 2%), asthenia (1% vs 1%), face edema (1% vs 0%), pain (2% vs 2%).

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

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

OVERDOSAGE

Experience with CARDURA© overdosage is limited. Two adolescents who each intentionally ingested 40 mg CARDURA© with diclofenac or paracetamol, were treated with gastric lavage with activated charcoal and made full recoveries. A two year-old child who accidently ingested 4 mg CARDURA© was treated with gastric lavage and remained normotensive during the five hour emergency room observation period. A six-month old child accidentally received a crushed 1 mg tablet of CARDURA© and was reported to have been drowsy. A 32 year old female with chronic renal failure, epilepsy and depression intentionally ingested 60 mg CARDURA© (blood level 0.9 μg/mL; normal values in hypertensives= 0.02 μg/mL); death was attributed to a grand mal seizure resulting from hypotension. A 39 year-old female who ingested 70 mg CARDURA©, alcohol and Dalmane© (flurazepam) developed hypotension which responded to fluid therapy.

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

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Pfizer U.S. Pharmaceuticals

Revised June 1997

A FIRST-LINE, FIRST-CHOICE SULFONYLUREA FOR TYPE 2 DIABETES

INSULIN-SPARING GLUCOSE CONTROL

ONCE-A-DAY

Amaryl®

glimepiride TABLETS

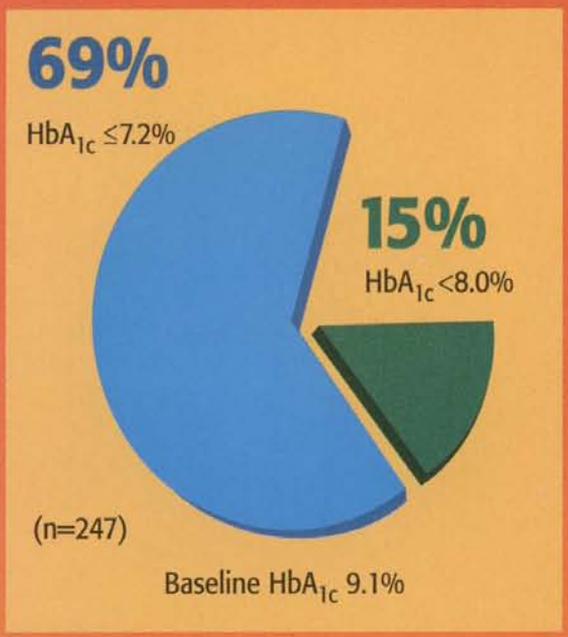
Please see brief summary of prescribing information on back.

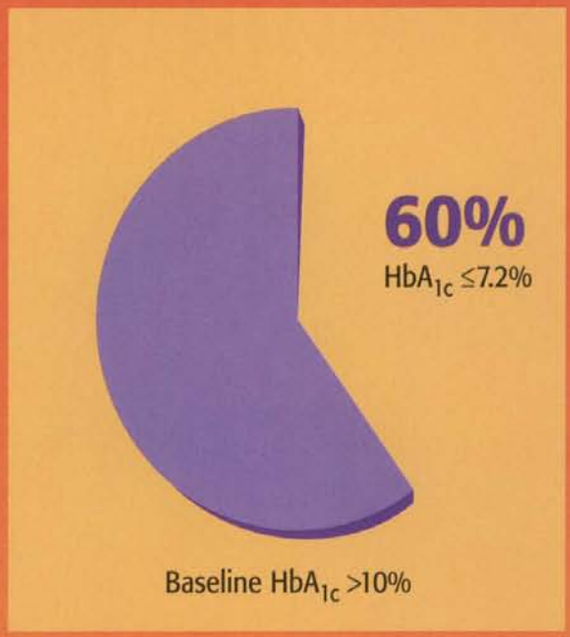
FEATURES LATEST CLINICAL RESULTS

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]



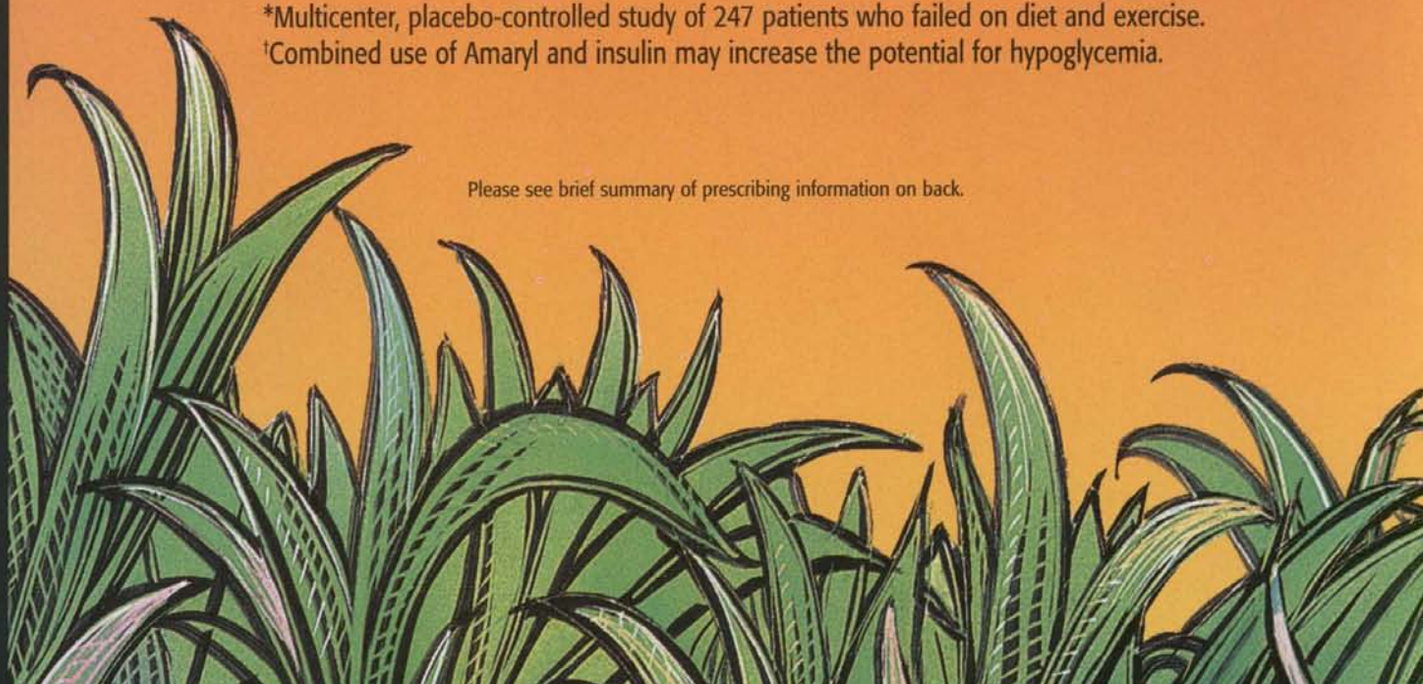


FAVORABLE SAFETY PROFILE

- 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

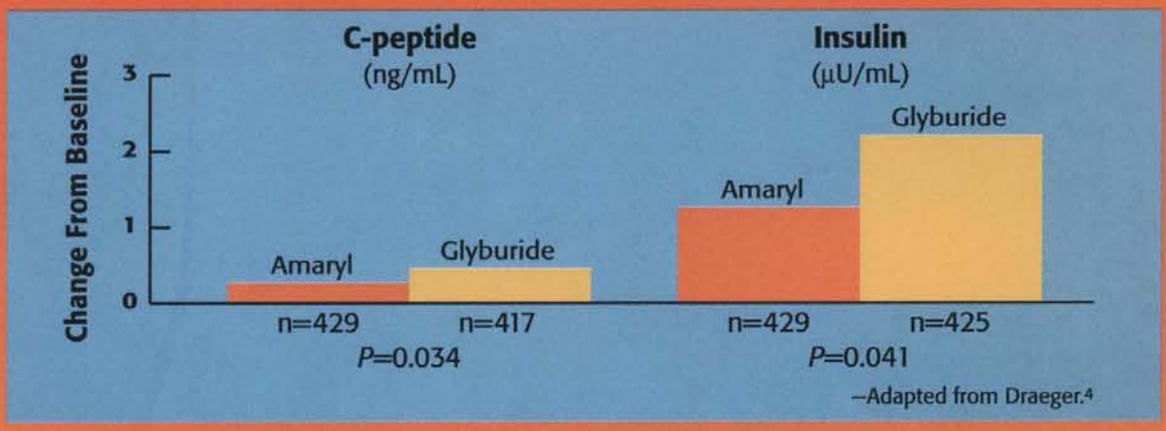
*Multicenter, placebo-controlled study of 247 patients who failed on diet and exercise.
†Combined use of Amaryl and insulin may increase the potential for hypoglycemia.

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[†]

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, Roßkamp 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.

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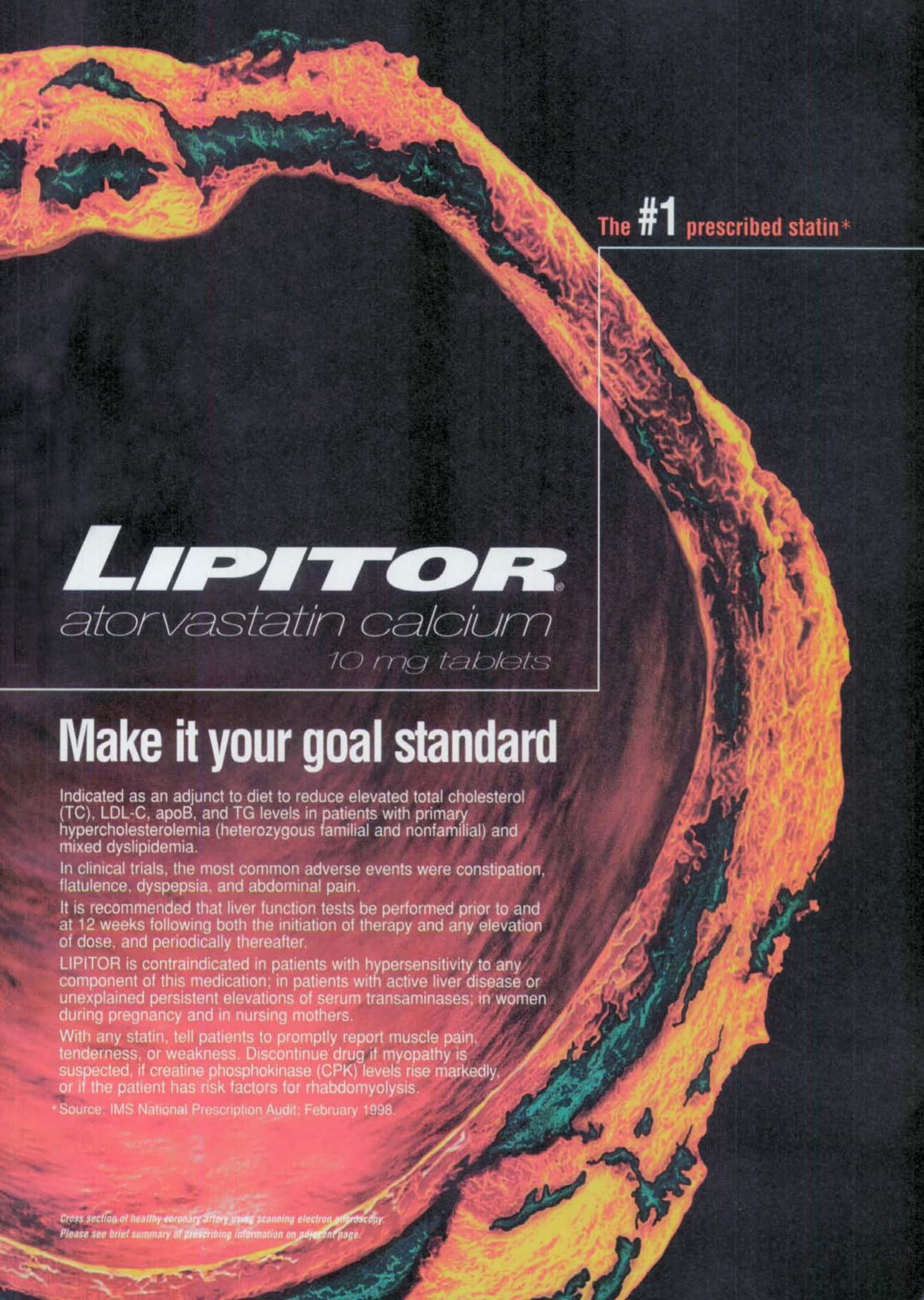
Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst
Kansas City, MO 64134

Hoechst



The #1 prescribed statin*

LIPITOR®
atorvastatin calcium
10 mg tablets

Make it your goal standard

Indicated as an adjunct to diet to reduce elevated total cholesterol (TC), LDL-C, apoB, and TG levels in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.

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

It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of 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.

With any statin, tell patients to promptly report muscle pain, tenderness, or weakness. Discontinue drug if myopathy is suspected, if creatine phosphokinase (CPK) levels rise markedly, or if the patient has risk factors for rhabdomyolysis.

*Source: IMS National Prescription Audit; February 1998.

Cross section of healthy coronary artery using scanning electron microscopy.
Please see brief summary of prescribing information on adjacent page.

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 prior to and at 12 weeks following both the initiation of therapy and any elevation of 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/m²). 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 causal relationship to drug include the following: angioneurotic edema and rhabdomyolysis.

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 February 1998

Manufactured by:
Warner-Lambert Export, Ltd. ©1997
Dublin, Ireland

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

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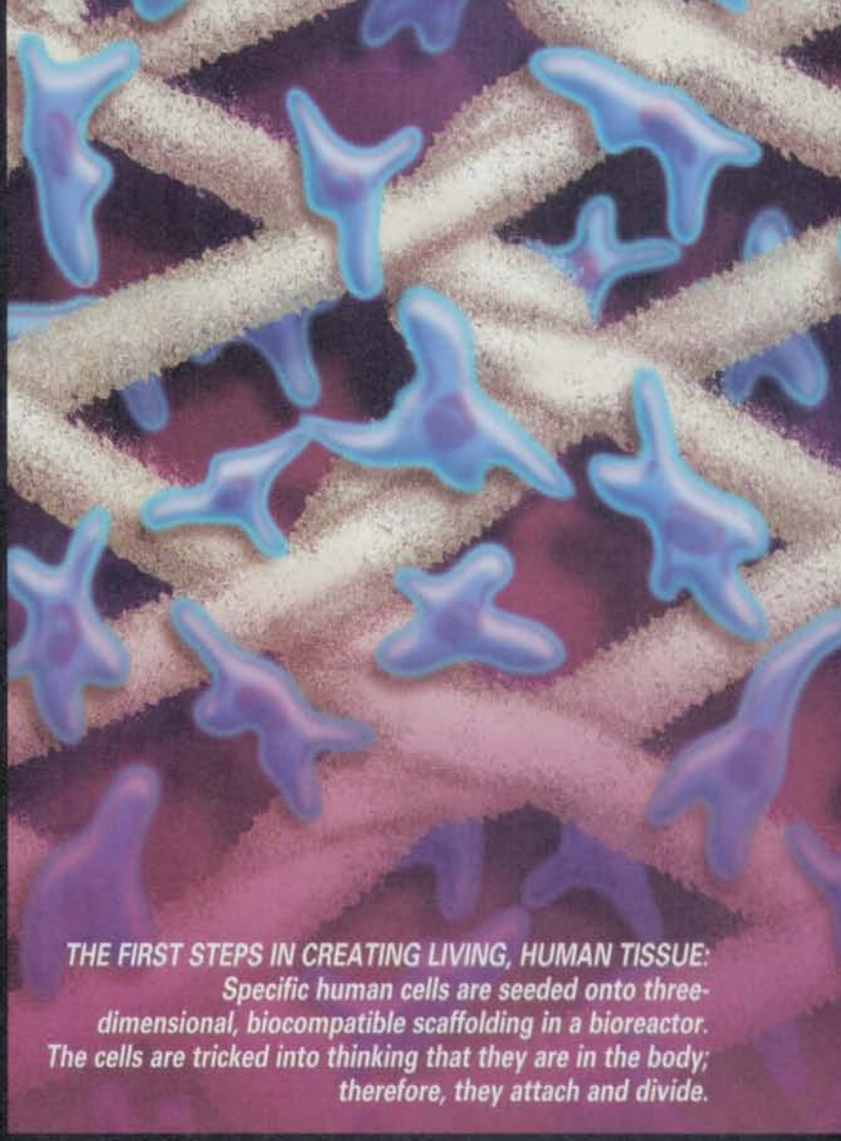

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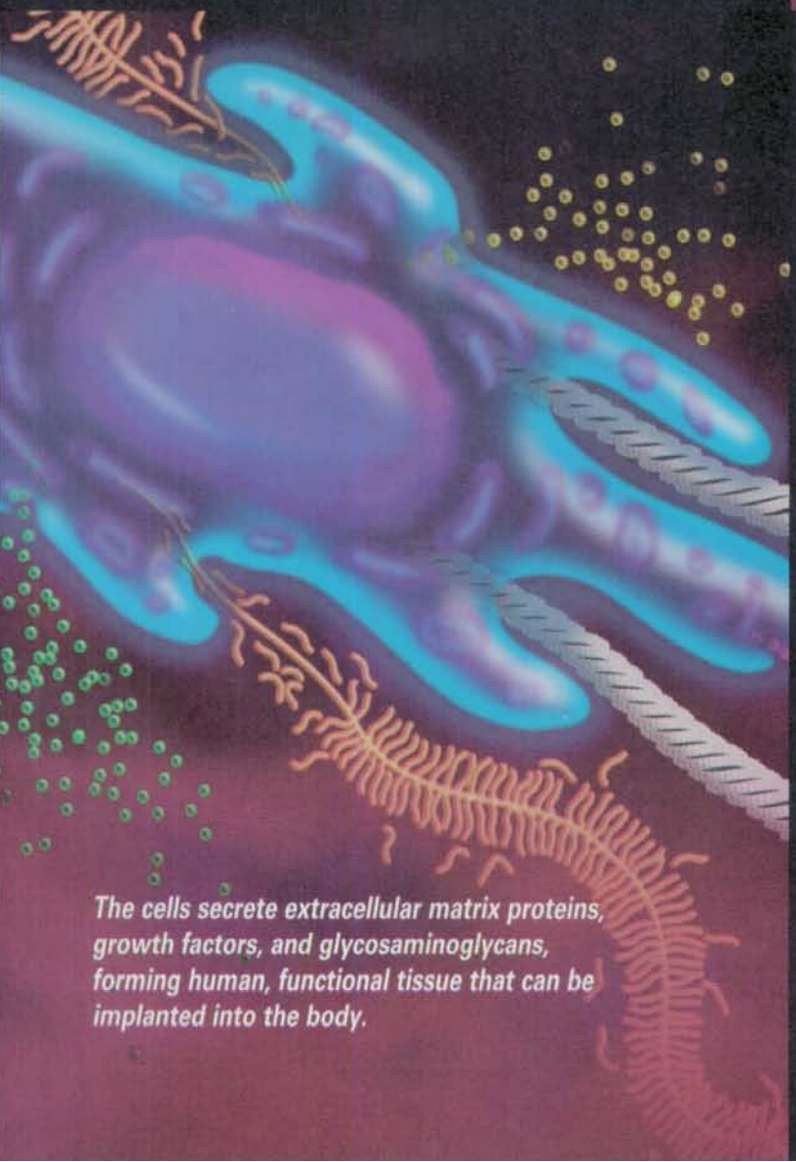

The cells secrete extracellular matrix proteins, growth factors, and glycosaminoglycans, forming human, functional tissue that can be implanted into the body.

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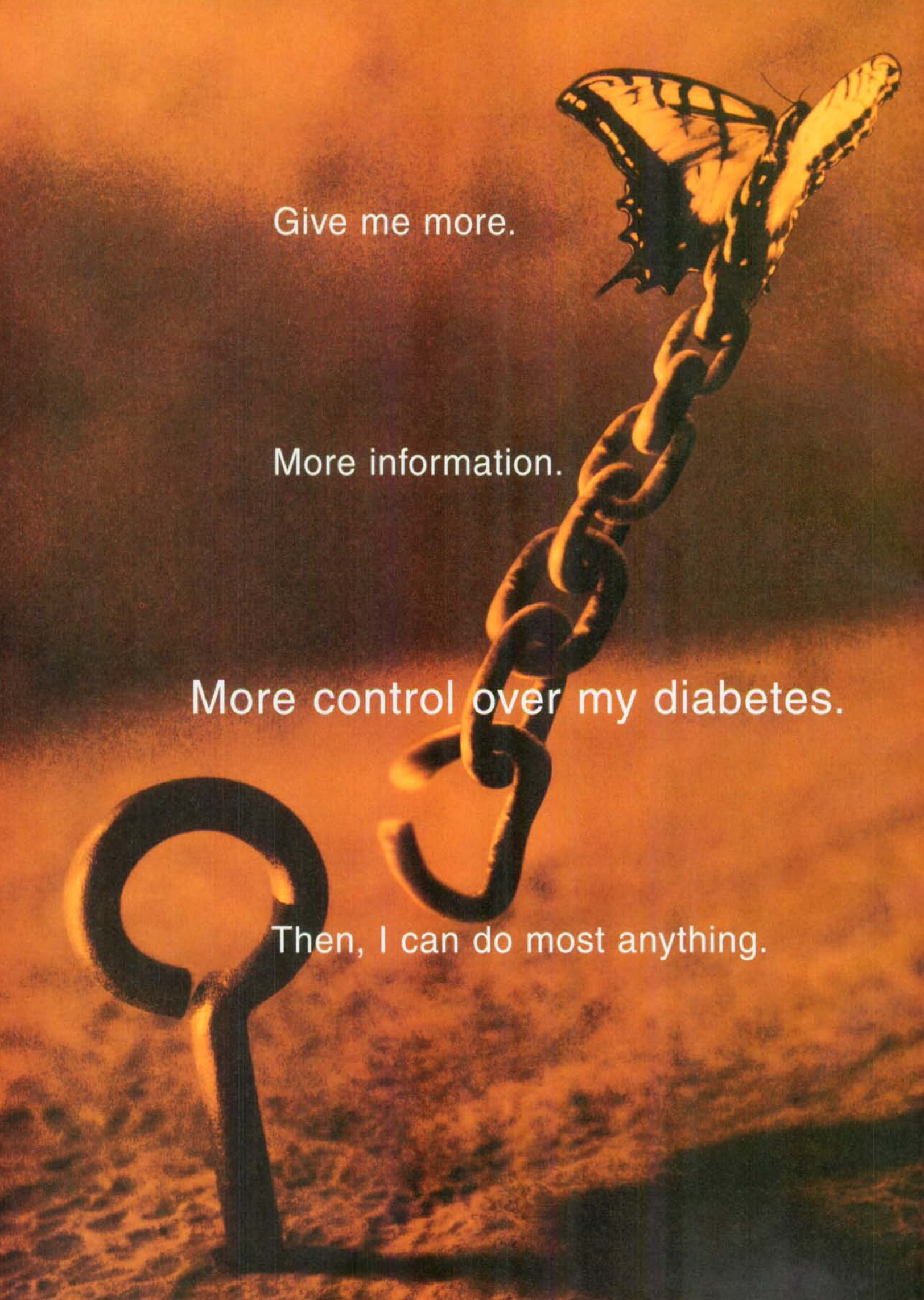
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More information.
More control over my diabetes.
Then, I can do most anything.

Now your patients can have all the information they need to control their diabetes with the new Accu-Chek™ Complete™ meter system, a powerful breakthrough in diabetes self-management. Unlike other meters, it does more than just test blood sugar. It records up to 1,000 values. And, with just the push of a button, it displays trends and averages on the meter screen without the need for a computer. In other words, it gives your patients the extra power they need to set themselves free.

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Humulin®
human insulin
(rDNA origin)

Good control may reduce the risk of complications

Insulin is essential

Lilly

Important safety information
Potential side effects associated with the use of all insulins include hypoglycemia, weight gain, hypokalemia, lipodystrophy, and hypersensitivity. **Starting or changing insulin therapy should be done cautiously and only under medical supervision.**

140 8

pre-meal glucose mg/dL % HbA_{1c}

ADA Clinical Practice Recommendations

Long-term glucose control in patients with type 2 diabetes may reduce the risk of complications.

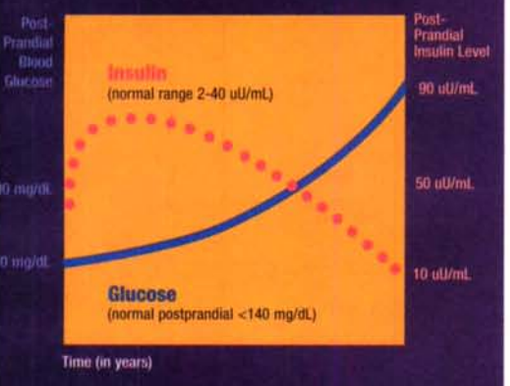
One study[1] of Japanese patients with type 2 diabetes showed a:

69% decrease in retinopathy

70% decrease in nephropathy

to life

Natural Progression of Untreated Type 2 Diabetes[2]

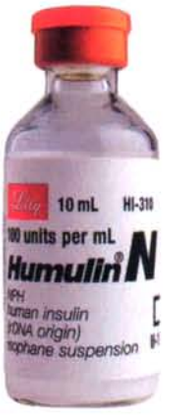


Over time, patients with type 2 diabetes produce less and less insulin[3] and, as a result, oral medications become limited in their ability to control blood glucose levels.

Among adults with type 2 diabetes, up to **58% will require exogenous insulin** with increasing duration of diabetes.[4]

A progressive disease requires progressive treatment

Only insulin can replace insulin



Humulin N at bedtime may be a good place to start.

Humulin N
NPH
human insulin
(rDNA origin)
isophane suspension

Humulin® is a registered trademark of Eli Lilly and Company.

References

1 Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diab Res Clin Pract.* 1995;28:103-117.

2 Adapted with permission from Staged Diabetes Management,™ ©International Diabetes Center, Minneapolis.

3 American Diabetes Association Consensus Statement. The pharmacological treatment of hyperglycemia in NIDDM. *Diabetes Care.* 1996;19(suppl 1):S54-S61.

4 *Diabetes 1996: Vital Statistics*. American Diabetes Association; 1996.

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Single-Topic Diabetes Resources

Contains 21 reproducible client handouts covering a variety of diabetes topics, and a professional guide for each sheet. Handouts are interactive, allowing you to tailor the teaching process and content to an individual's needs. Also ideal for diabetes education classes.

Each 2-sided handout follows a standard format. The first section covers self-assessment, rationale for learning about the topic, and learning objectives. Topic-specific information comes next. The last section focuses on goal-setting, monitoring, and problem solving.

The professional guides help you assess the need for and timing of content, and provide you with supplemental information, such as ideas for gathering assessment data; creative ways to increase interactivity; additional learning objectives; and client and professional resources. #5503-01

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Facilitating Lifestyle Change: A Resource Manual

A great resource to help you effect positive behavioral change in your patients with diabetes. This valuable tool approaches lifestyle change through a four-step model—Assessment, Goal Setting, Intervention, and Evaluation—and features a series of reproducible master forms to facilitate data collection and monitoring.

Manual includes detailed professional information on how best to use each form to benefit the individual patient, including tips for uses in different settings. It also contains a collection of case studies which demonstrate different ways the monitoring forms can be used with various types of clients. And its appendices contain extensive charts, tables and other resources. #5505-01

Nonmember: $22.95
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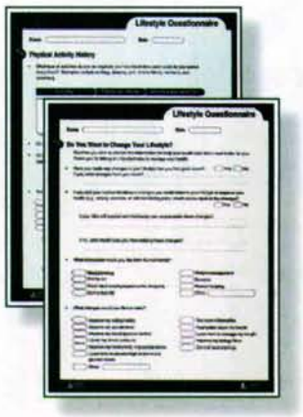
Contents:

The Lifestyle Change Process • How to Use Lifestyle Change Resources • Case Studies • Anthropometric Data • Biochemical Indices/Laboratory Data • Assessment of Nutrition Knowledge • Assessment of Nutrient Intake •



Weight Control Readiness Scale • Compulsive Eating and Stress Management Resources • Goal Setting • Diabetes Nutrition Intervention Resources • Physical Activity Intervention Resources • Weight Management/ Behavior Change Resources • Lifestyle Questionnaire • Eating Behavior Diary • Lifestyle Change Plan • Food and Physical Activity Record • Summary Record

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American Diabetes Association.

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

Rx only

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 creatine 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 C_{max} 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, C_{max}, and T_{max} 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) involving 6595 patients treated with PRAVACHOL (N=3302) or placebo (N=3293) for a median of 4.8 years and in the Cholesterol and Recurrent Events (CARE) study, involving 4159 men and women treated with PRAVACHOL (N=2081) or placebo (N=2078) for an average of 4.9 years the adverse event profile in the PRAVACHOL (pravastatin sodium) group was comparable to that of placebo for the duration of the studies. 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.

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DATA, RESULTS AND CONSEQUENCES OF MAJOR TRIALS WITH FOCUS ON TYPE 2 DIABETES

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Type 2-diabetes world-wide according to new definition.

Peter Bennett
How to prevent Type 2-diabetes.

Wilfred Y. Fujimoto
Background and recruitment data for the US Diabetes Prevention Project.

Rodolfo Paoletti
The pleiotropic effect of statins in atherosclerosis and diabetes.

Hans Henrik Parving
Beneficial effect of Ramipril on LVH in Type 2-diabetic patients.

Motoaki Shichiri
Long-term results of the Kumamoto Study on optimal diabetes control in Type 2-patients.

Stein Vaaler
Optimal glycemic control in Type 2-patients including insulin-treatment: better outcome?

Ramon Gomis de Barbara
Oral agents in controlling Type 2-diabetes.

Hertzel C. Gerstein
Data from the Hope and Microhope studies.

Michel Marre
The Diab-Hycar study, an update.

Werner Bachmann
OAD-Insulin combination in the treatment of Type 2-diabetes

September 8:

Jay S. Skyler
Can we translate DCCT-results to Type 2-patients?

George Steiner
The Diabetes Atherosclerosis Intervention Study.

Niels de Fine Olivarius
The Danish Study, Diabetes Care in General Practice.
A 6 year randomised trial of intensified versus standard physician care.

Oluf B. Pedersen
4 years follow-up from the Steno-Study in Type 2-patients with microalbuminuria with an intensified multifactorial intervention programme.

Ed Lewis
Trial on nephropathy in diabetes, valid for both types of diabetes?

Robert W. Schrier
New results from the A-B-C-D study on blood pressure control in Type 2-diabetes.

Michel Lievre
Meta-analysis of antihypertensive treatment on cardiovascular prevention in Type 2-diabetes.

Philippe Moulin
Combined analysis of lipid interventions in Type 2-diabetes.

Philippe Passa
Conclusion

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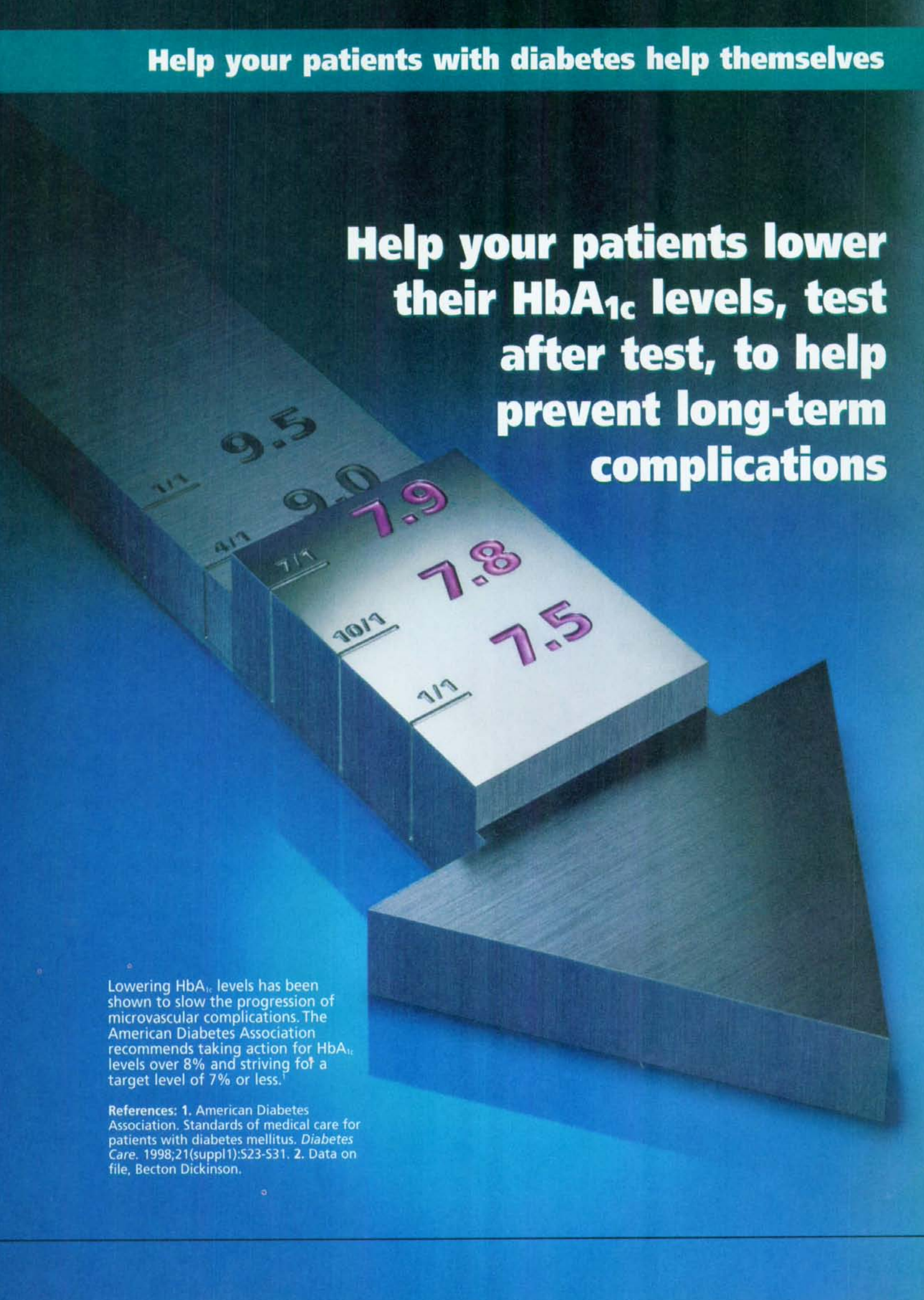

Lowering HbA_{1c} levels has been shown to slow the progression of microvascular complications. The American Diabetes Association recommends taking action for HbA_{1c} levels over 8% and striving for a target level of 7% or less.[1]

References: 1. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care.* 1998;21(suppl1):S23-S31. **2.** Data on file, Becton Dickinson.

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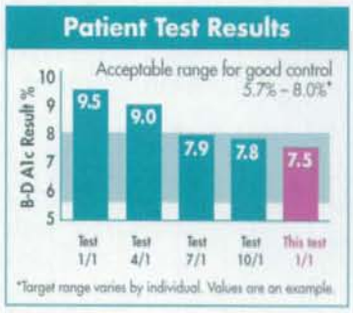

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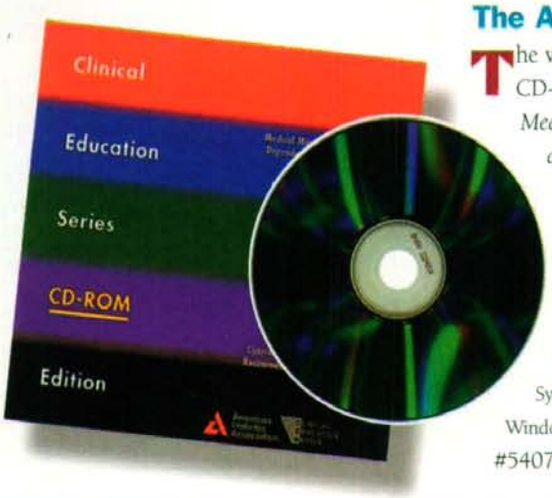

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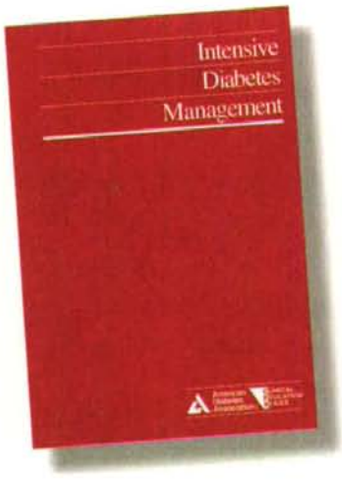

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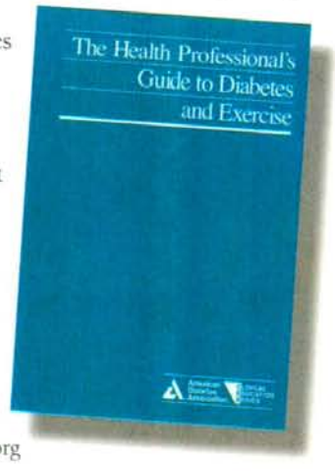

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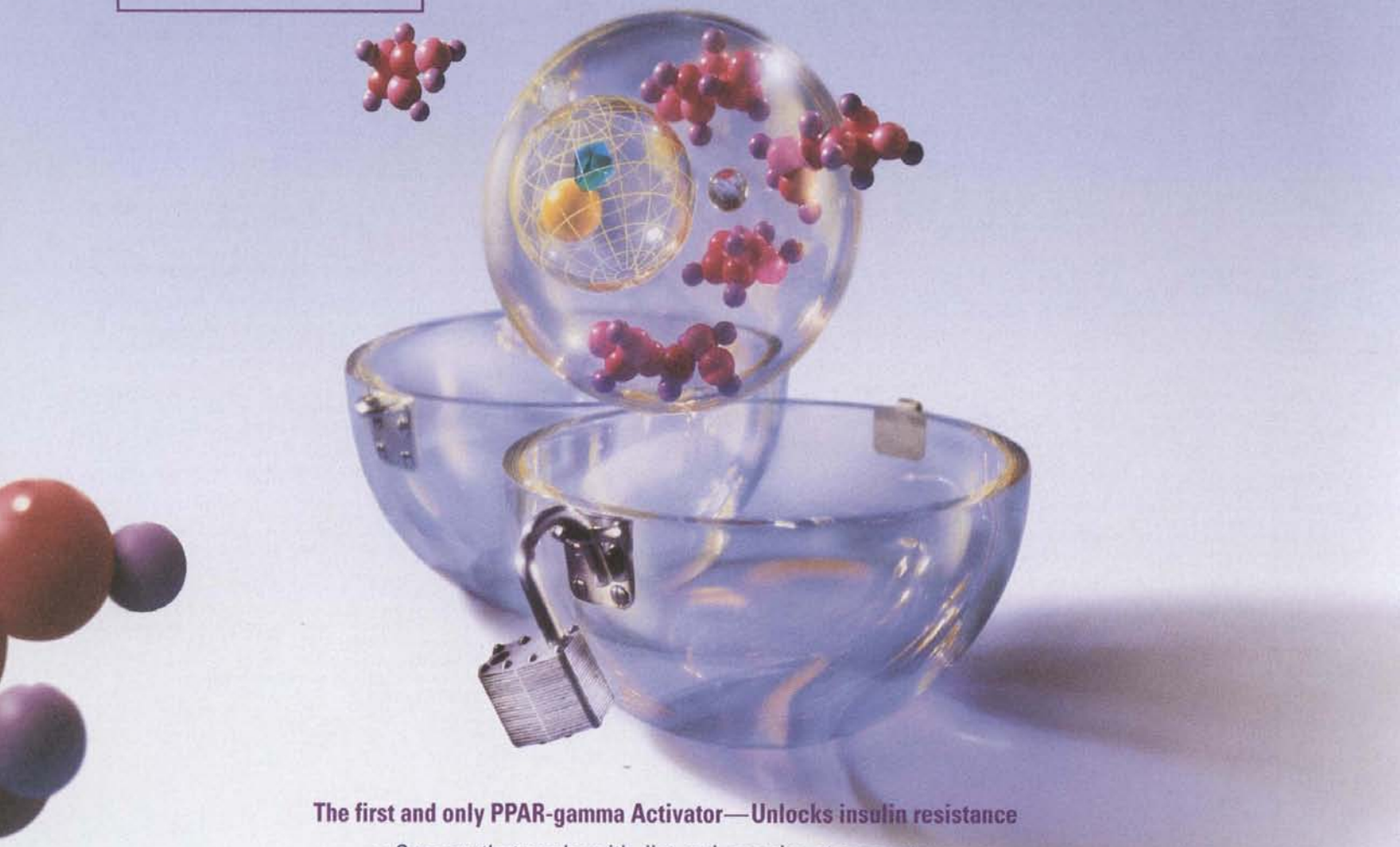

The first and only PPAR-gamma Activator—Unlocks insulin resistance

- 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

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**.

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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 or hepatitis 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.
Rx only

February 1998

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Vega Baja, PR 00694
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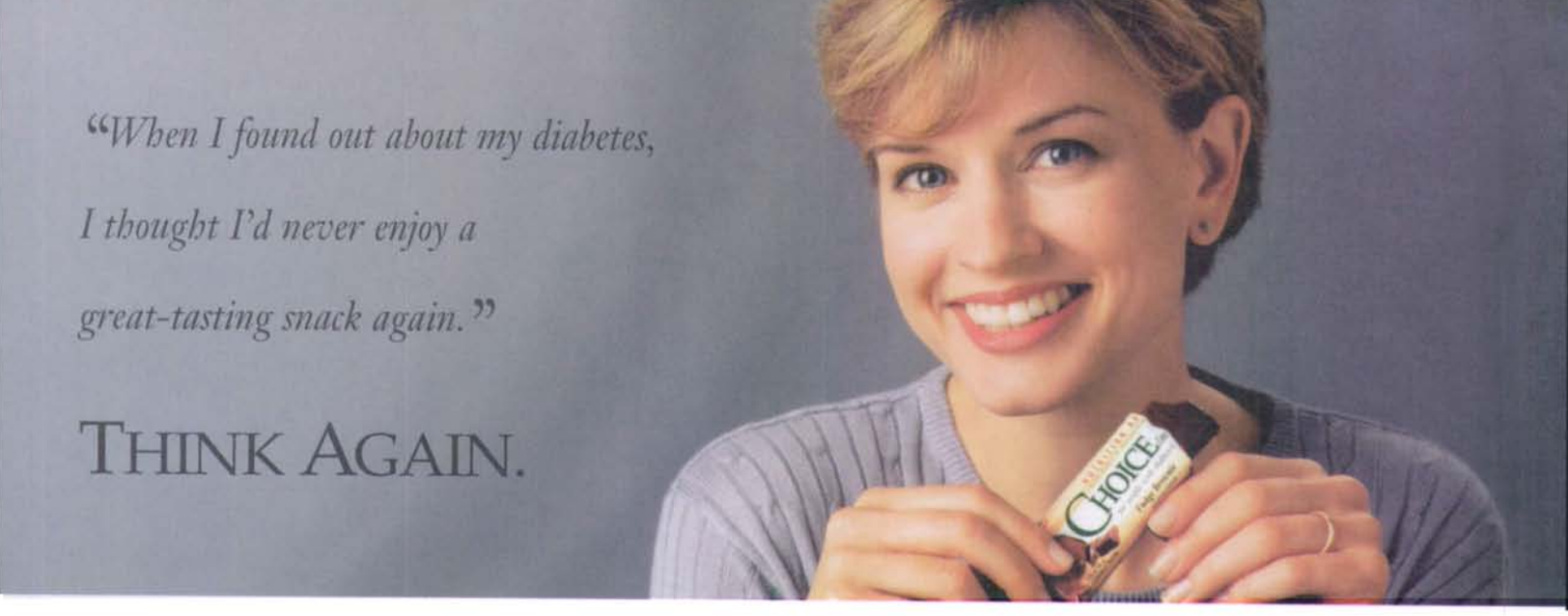

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