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Diabetes Care

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Combined use of a fasting plasma glucose concentration and HbA_{1c} or fructosamine predicts the likelihood of having diabetes in high-risk subjects

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American Diabetes Association.

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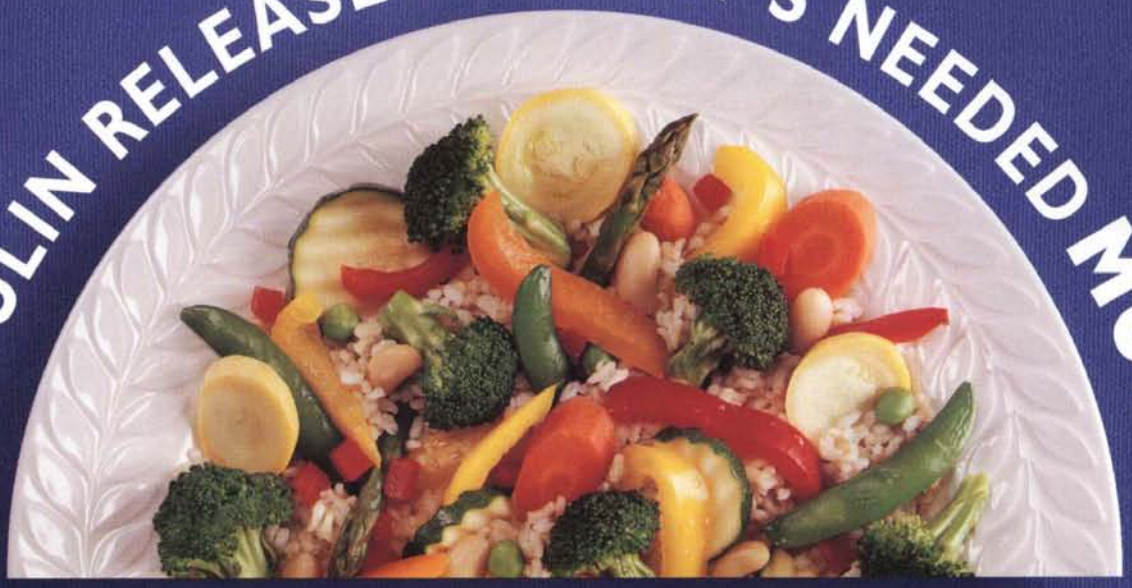

WITH LESS DURING FASTING HOURS[1-3]

For your patients with type 2 diabetes: once-a-day Glucotrol XL for the glucose control they need, with lower fasting insulin than glyburide and immediate-release glipizide[1-3]

- Long-term data show no weight gain[1]*
- No adverse effect on the lipid profile[4]
- Least expensive branded oral hypoglycemic agent[5†]

WHEN DIET ALONE FAILS IN TYPE 2 DIABETES...
ONCE DAILY GLUCOTROL XL® (glipizide) extended release tablets 5 mg and 10 mg GITS

ONCE-A-DAY CONVENIENCE WITH LOWER FASTING INSULIN

As with all sulfonylureas, hypoglycemia may occur.

* Median duration of treatment in long-term studies with 564 participants was 25.5 months.

† Cost to the pharmacist based on wholesale price (AWP) listings in *PriceAlert*™, January 15, 1998 (actual cost to patients may vary).

References: 1. Data on file. Pfizer Inc, New York, NY. **2.** Berelowitz M, Fischette C, Cefalu W, Schade DS, Sutin T, Kourides IA. Comparative efficacy of a once-daily controlled-release formulation of glipizide and immediate-release glipizide in patients with NIDDM. *Diabetes Care*. 1994;17:1460-1464. **3.** Burge MR, Schmitz-Fiorentino K, Fischette C, Qualls CR, Schade DS. A prospective trial of risk factors for sulfonylurea-induced hypoglycemia in type 2 diabetes mellitus. *JAMA*. 1998;279:137-143. **4.** Blonde L, Guthrie RD Jr, Tive L, Fischette C, the Glipizide GITS Efficacy and Safety Trial Study Group. Glipizide GITS is effective and safe in a wide range of NIDDM patients: results of a double-blind, placebo-controlled efficacy and safety trial. *Diabetes*. 1996;45(suppl 2):285A. **5.** *PriceAlert*™, San Bruno, Calif: First DataBank; January 15, 1998;10:7,25,37,54,68,74.

Please see brief summary of prescribing information on adjacent page.

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. Some patients fail to respond or gradually lose their responsiveness to sulfonylurea drugs, including Glucotrol XL. In these cases, the addition of another oral blood glucose-lowering agent to Glucotrol XL therapy can be considered. Other approaches that can be considered include substitution of Glucotrol XL therapy with that of another glucose lowering agent or insulin. Glucotrol XL should be discontinued if it no longer contributes to glucose lowering. Judgment of response to therapy should be based on regular clinical and laboratory evaluations.

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. Therapy with a combination of glucose-lowering agents may increase the potential for 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 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. When Glucotrol XL is used in combination with another glucose-lowering agent, the second agent should be added at the lowest recommended dose and patients should be observed carefully. Titration of the second agent should be based on clinical judgment.

More detailed information available on request.

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

Symposium before the EASD meeting, Barcelona *Centro de Convenciones*

SEPTEMBER 7+

PROGRAM

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Combined analysis of lipid interventions in Type 2-diabetes.

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Conclusion

Supported by an educational grant
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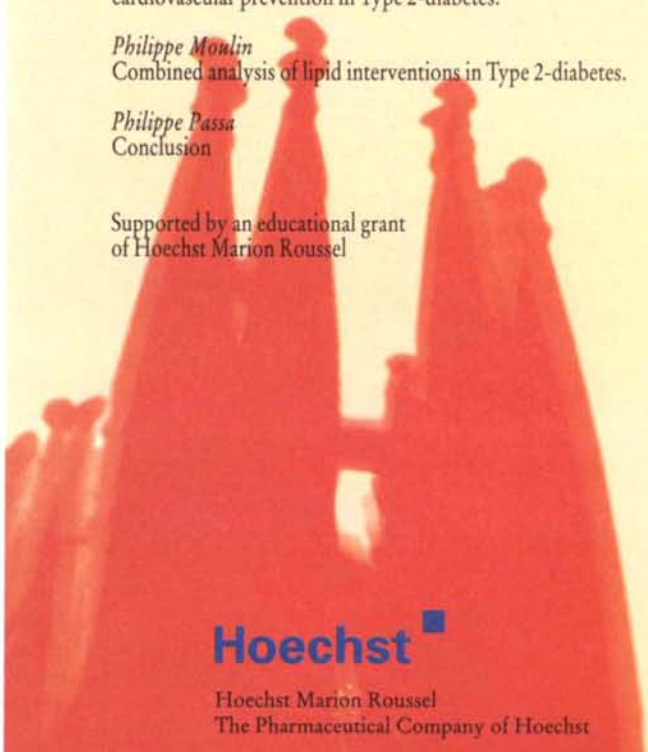

Please contact:
BC Best Concept GmbH
Max-Planck-Straße 38
D-63150 Heusenstamm
Germany

Weronika Bugge
Tel. +49 6104 101022
Fax +49 6104 2010

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VOLUME 21 NUMBER 8

Diabetes Care

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

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

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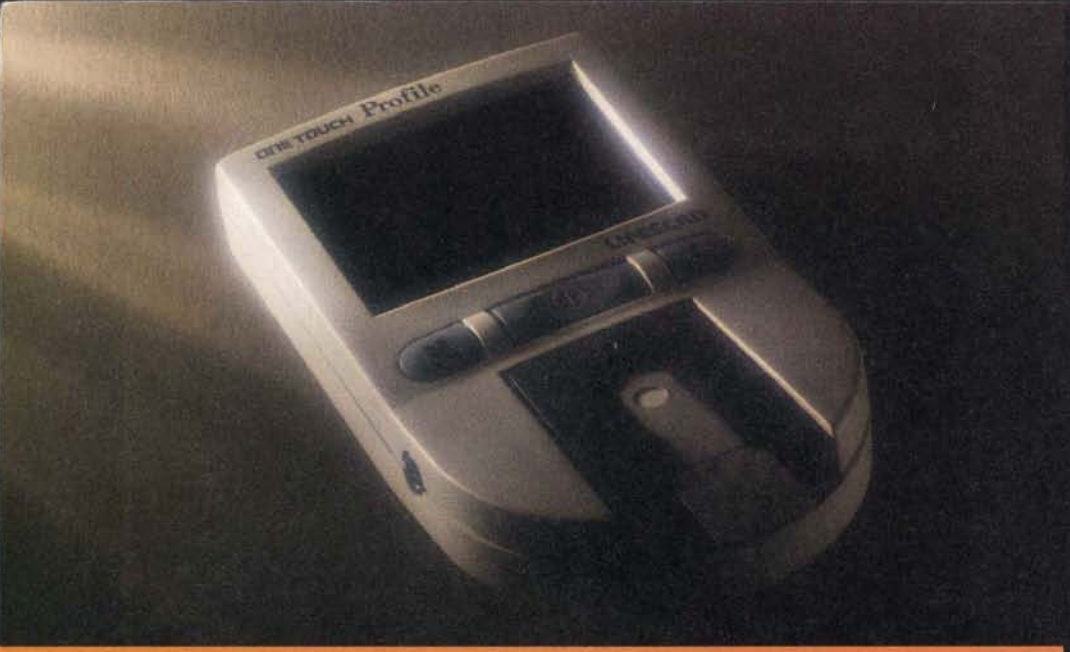

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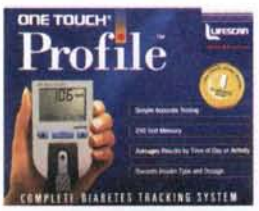

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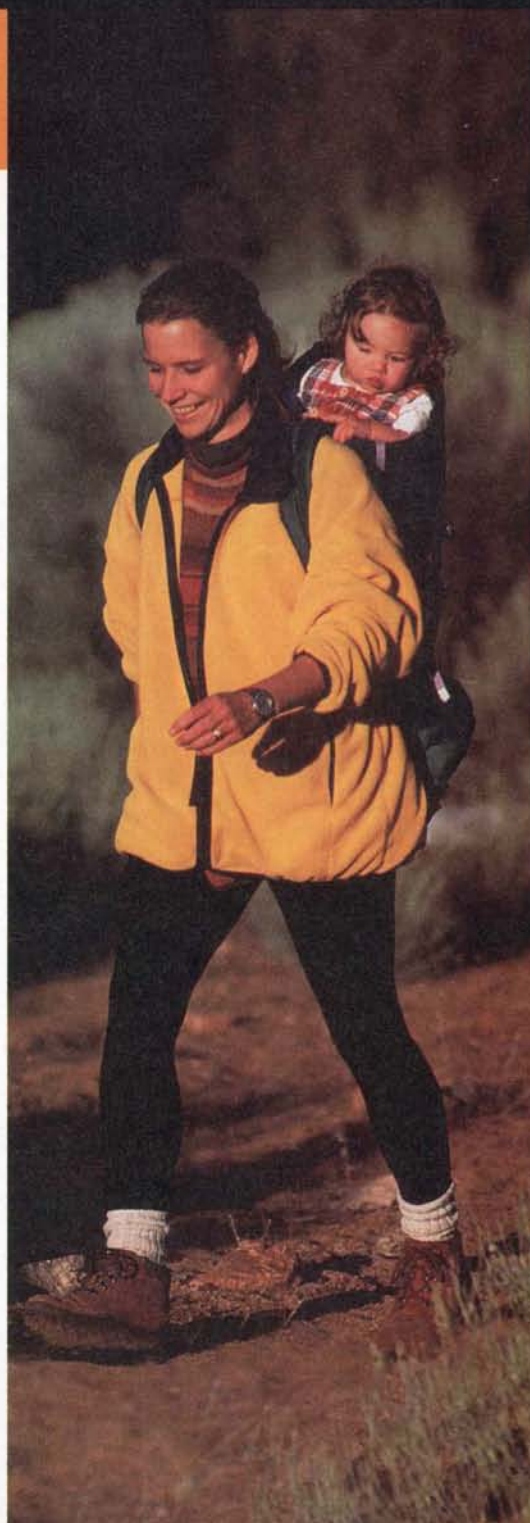

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Announcing an educational symposium to be ***held immediately prior to*** *the Annual Meeting of the American Association of Diabetes Educators in Minneapolis, Minnesota*

WEDNESDAY, AUGUST 19, 1998

CURRENT AND FUTURE PHARMACOLOGIC STRATEGIES IN TREATING OBESITY

10:30AM–12:30PM • Hyatt Regency Minneapolis, Greenway Ballroom

Lunch: 12:30PM–1:30PM

Overview of Obesity Treatment in Patients With Diabetes

MARION J. FRANZ, MS, RD, LD, CDE

Director of Professional Education and Nutrition • *International Diabetes Center Minneapolis, Minnesota*

Pharmacologic Management of Obesity in Patients With Diabetes

DAVID E. KELLEY, MD

Associate Professor of Medicine • *Division of Endocrinology and Metabolism University of Pittsburgh School of Medicine*

Chief of Endocrinology • *Veterans Administration Medical Center • Pittsburgh, Pennsylvania*

Integrating Pharmacotherapy in an Overall Treatment Program

ANNE WOLF, MS, RD

Director of Nutrition • *The Women's Place • University of Virginia Health Sciences Center Charlottesville, Virginia*

Evolving Strategies in the Treatment of Obesity

MICHAEL W. SCHWARTZ, MD

Head • *Section of Clinical Nutrition*

Associate Professor • *Division of Metabolism, Endocrinology and Nutrition Department of Medicine • University of Washington • Seattle, Washington*

Registration

To register by phone, call ***1-800-457-9925*** *or fax your name, title, institution, and address to* ***212-645-6844.*** *Please mention the key phrase "AADE."*

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

Continuing Education Credit

This program for 2 contact hours has been approved by the American Association of Diabetes Educators (AADE), which is accredited as an approver of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation. Approval of this Continuing Education Activity does not imply endorsement by the AADE.

The Commission on Dietetic Registration, the credentialing agency for the American Dietetic Association, has approved this program for 2 contact hours.

ACPE®

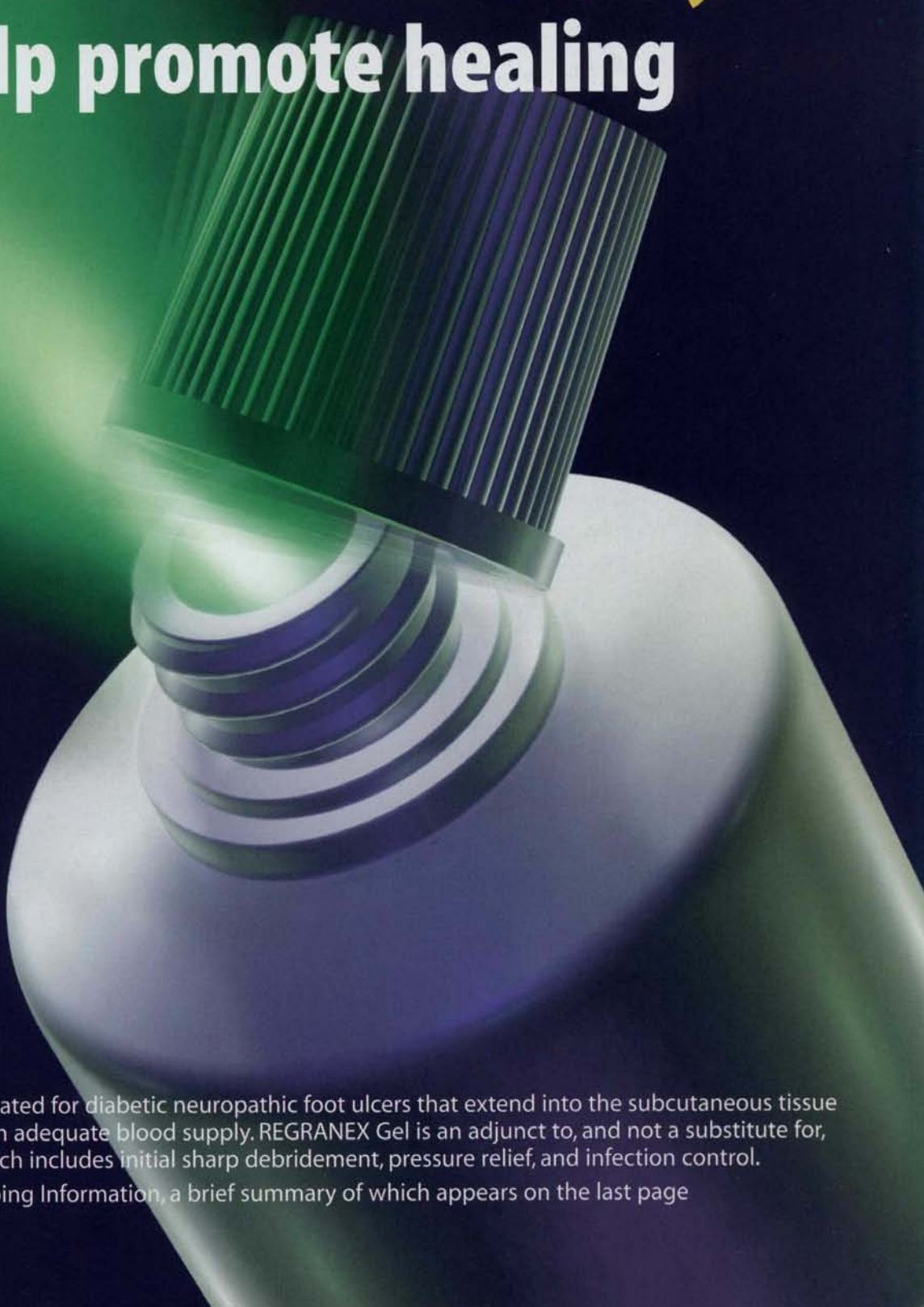
The American Association of Diabetes Educators is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Universal Program Number: 069-000-98-102-L01. This program provides 2 contact hours (.2 CEUs) of continuing education credit.

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

For diabetic neuropathic foot ulcers...*

REGRANEX® GEL 0.01%
(becaplermin)

An innovation to *actively* help promote healing



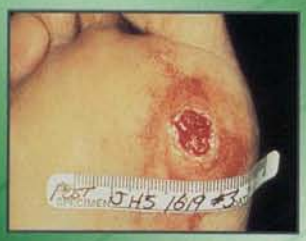
* REGRANEX Gel is indicated for diabetic neuropathic foot ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. REGRANEX Gel is an adjunct to, and not a substitute for, good wound care, which includes initial sharp debridement, pressure relief, and infection control.

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

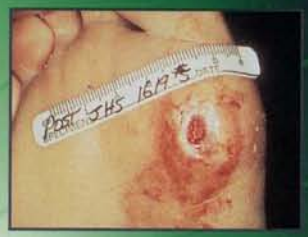
HELP PROMOTE HEALING

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

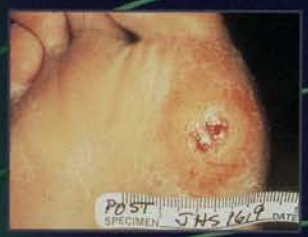
Case study results



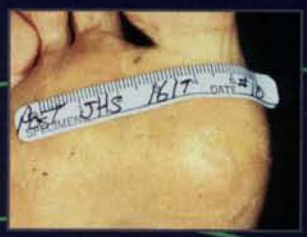
After debridement followed by 1 week of REGRANEX Gel plus good wound care



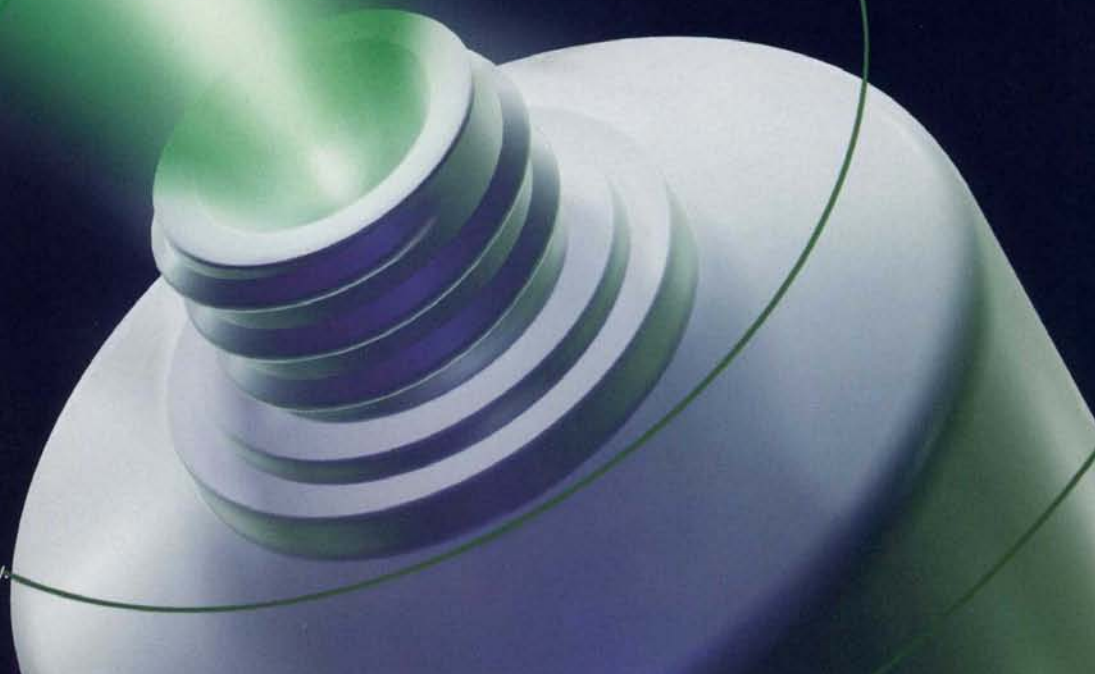
After 3 weeks of REGRANEX Gel plus good wound care



After 6 weeks of REGRANEX Gel plus good wound care

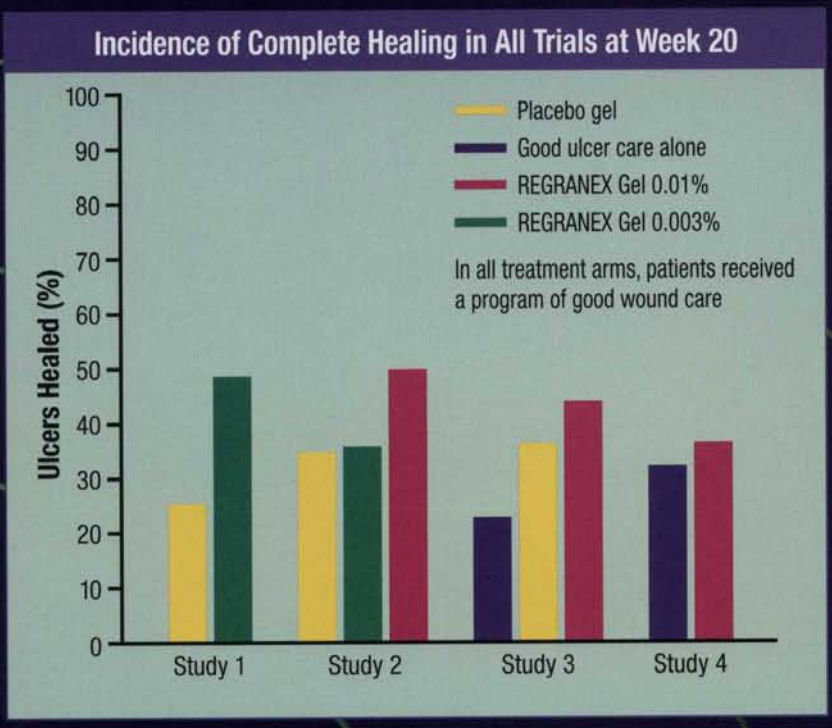


After 11.5 weeks of REGRANEX Gel plus good wound care*



* Color only adjusted for consistency.

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



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 only been studied in the treatment of diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond (Stage III or IV, 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
- Systemic treatment of infection
- Initial and ongoing debridement
- Moist dressings changed twice a day
- Proper nutrition and hydration
- Off-loading of pressure on wound

For more information, call our professional support line at
1-888-REGRANEX

Please visit our website at
www.regranex.com

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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Raritan, New Jersey 08869

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 Revised February 1998 635-10-240-2B

ORTHO-McNEIL

TRANSFORMING WOUND CARE TO WOUND HEALING

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

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NOW

In type 2 diabetes

TURN ON THE PRANDIAL POWER™

Introducing a physiological approach to glycemic control

First of a new class–the meglitinides

PRANDIN stimulates prandial insulin release from functioning pancreatic beta cells to lower elevated glucose levels with a low risk of severe hypoglycemia.* Glucose-lowering effect follows the prandial insulin surge, when dosed preprandially at each of two, three, or four meals.[1]

With PRANDIN, as with all blood glucose-lowering agents, hypoglycemia may occur. The most common other side effects reported were cold- and flu-like symptoms, headache, diarrhea, joint ache, and back pain.

An adjunct to diet and exercise

PRANDIN™
repaglinide TABLETS

INSULIN-RELEASING POWER WHEN YOU NEED IT™

*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.

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

NOW

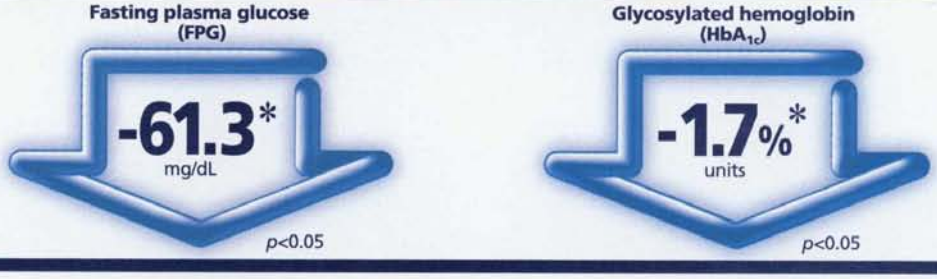
In type 2 diabetes

PRANDIN™

TURN ON THE PRANDIAL POWER™

Effective first-line therapy

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

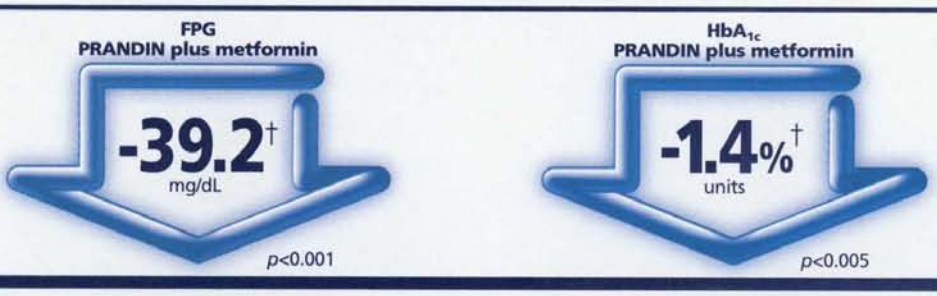


* Represents change between placebo and PRANDIN: FPG (placebo=+30.3 mg/dL, PRANDIN=-31 mg/dL); HbA_{1c} (placebo=+1.1% units, PRANDIN=-0.6% units).

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

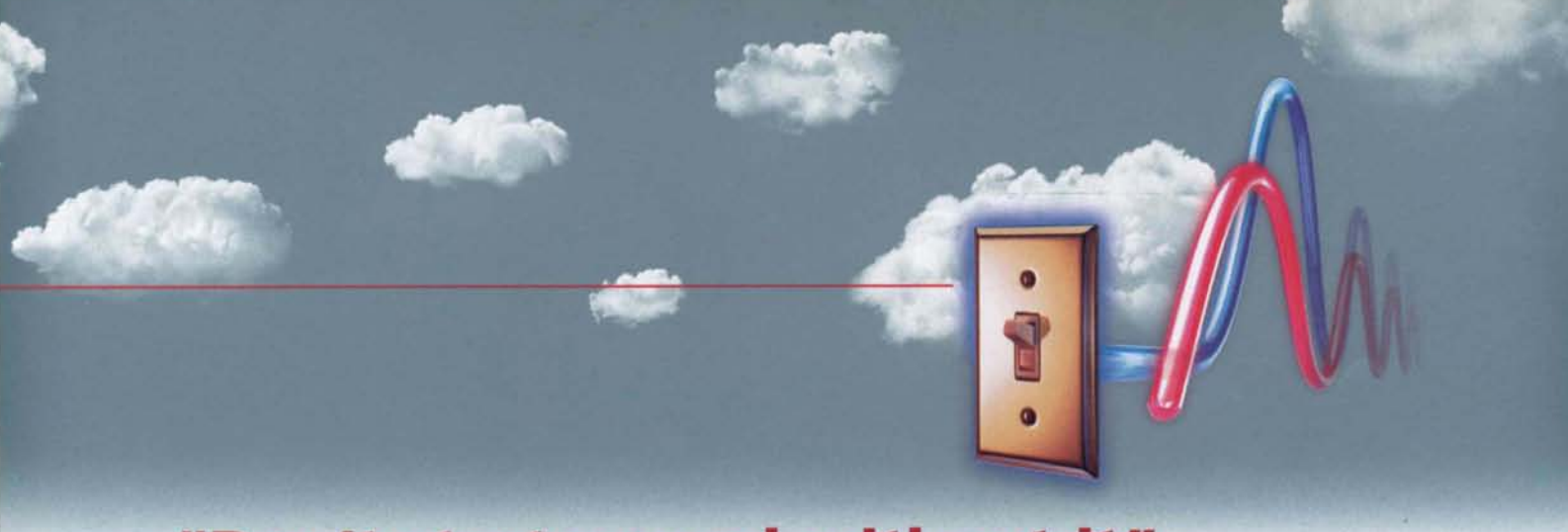
Significant reductions *vs* baseline in patients who previously failed on metformin alone[1]



†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.



"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.

The UGDP study suggested increased cardiovascular risk with oral antidiabetic agents.

An 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.

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.

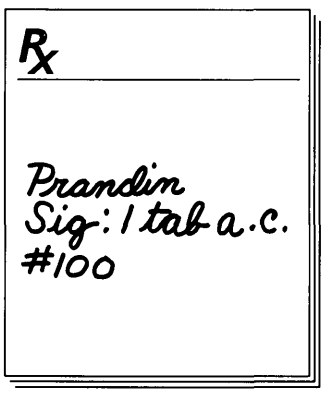
Geriatric Use: In repaglinide clinical studies of 24 weeks or greater duration, 415 patients were over 65 years of age. In one-year, active-controlled trials, no differences were seen in effectiveness or adverse events between these subjects and those less than 65 other than the expected age-related 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.

123695R July 1998

Novo Nordisk

Schering

Amazingly Simple

Quick, accurate, lab-comparable results without a single button to push!

And because the meter uses only the tiniest drop of blood (3 µL), there is no need for painful finger squeezing and hanging drops of blood. With self-monitoring made this simple, patients may just test more often.

Simply Amazing

A finger-friendly test strip that does most of the work!

It not only starts the meter, but also sips in the small amount of blood needed for an accurate result. That helps minimize errors and retesting, leading to more consistent accuracy and improved diabetes management.

GLUCOMETER ELITE®

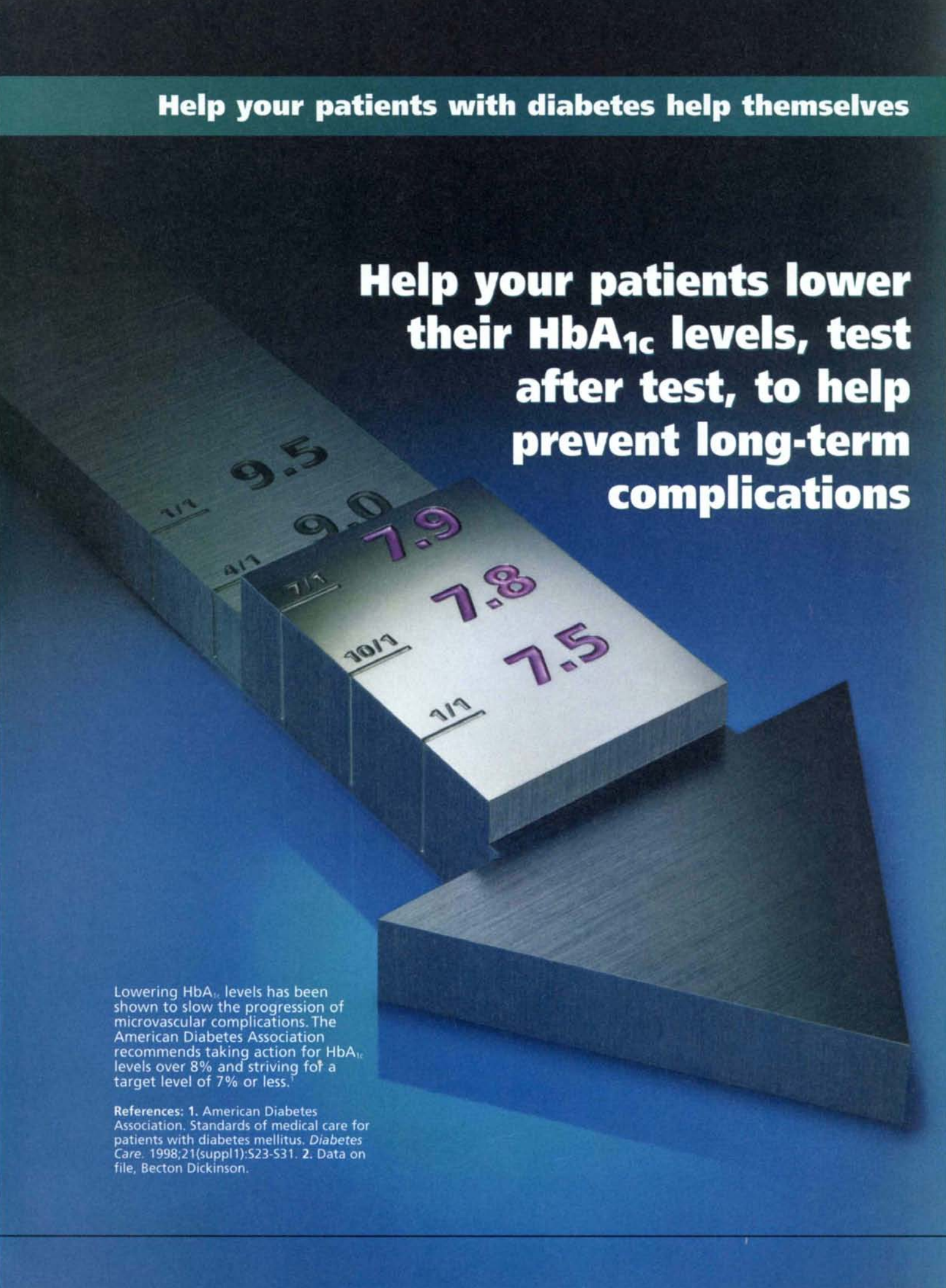
Diabetes Care System

Simply Brilliant

Bayer

Help your patients with diabetes help themselves

Help your patients lower their HbA_{1c} levels, test after test, to help prevent long-term complications



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.

New from B-D™

The B-D A1c At-Home Test kit can help your patients manage their diabetes more confidently

Accurate

Comparable accuracy and precision to laboratory or in-office HbA_{1c} testing (CV 3.9%) with just 2 drops of dried blood[2]

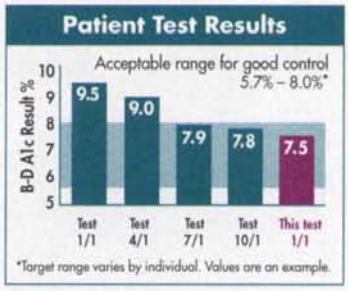
Convenience/Compliance

More convenient than conventional testing methods that can require additional trips to laboratory or office

- Increased convenience may improve testing compliance

Promotes Interaction

You and your patients receive test results within about 2 weeks, so you can review results at regularly scheduled visits



The American Diabetes Association recommends reevaluation of therapy when HbA_{1c} levels are >2% points above normal (non-diabetes) range.[1]

Automatic Enrollment

Patients can be automatically enrolled in the B-D A1c mail program

- Patients can receive new test kit every 3 or 6 months
- Arrival of each new test kit reminds patients to perform next B-D A1c At-Home Test

Recommend the B-D A1c At-Home Test kit and help your patients maintain good control and prevent long-term complications. Call 1·888·367-9539 for more detailed product information.

Visit our Web site at *www.BD.com/diabetes*

NEW

B-D A1c At-Home Test™

TO MANAGE DIABETES MORE CONFIDENTLY™

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 98A1CD035E0 April 1998

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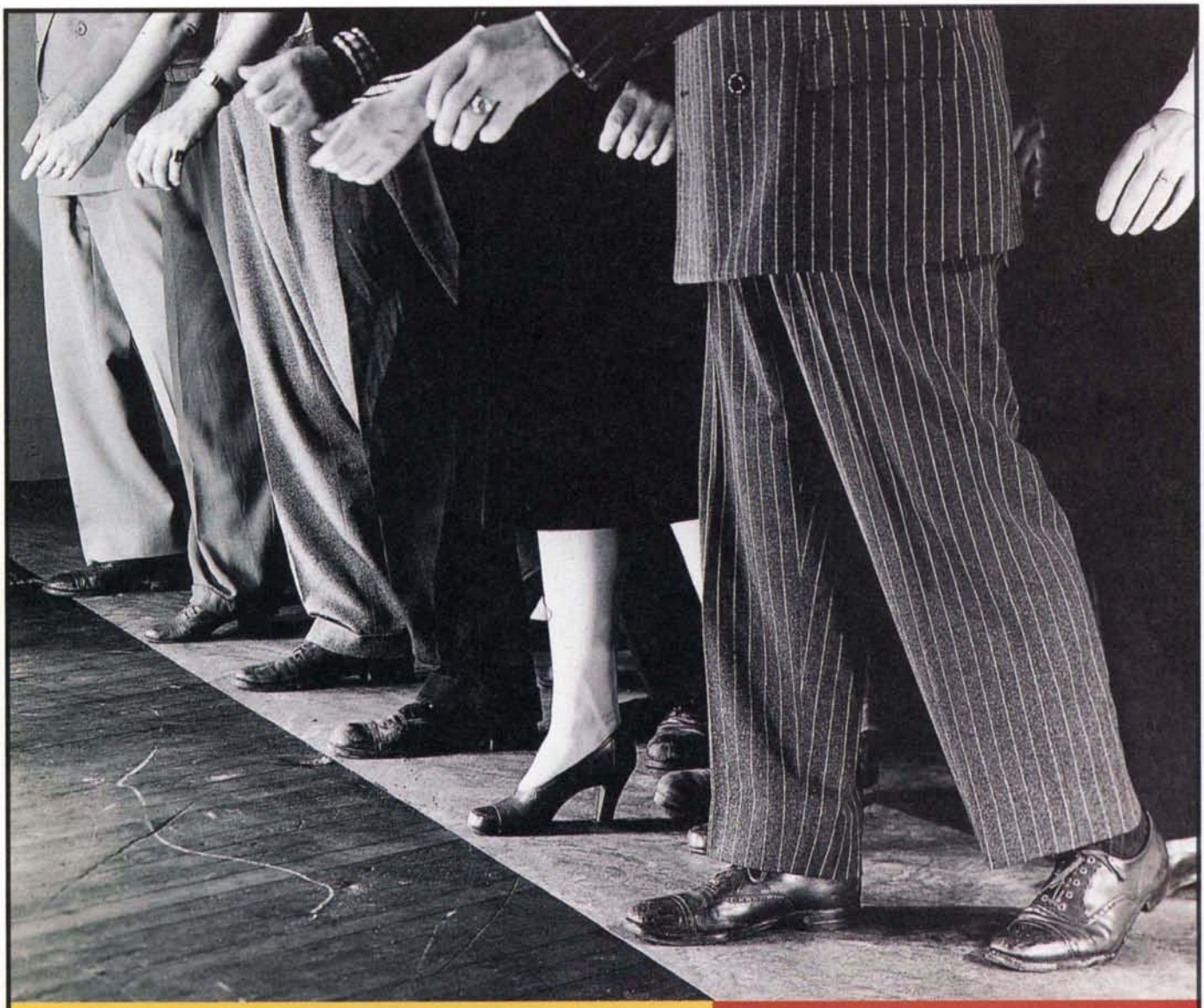


The average person walks 63.4 miles a week.

A few more miles could save a life.

Diabetes kills more people than AIDS or breast cancer. But you can help stop it. Join America's Walk for Diabetes, happening in over 300 locations nationwide the weekend of October 3rd.* Gather co-workers, friends, and family and walk for a cure. Call for more information and to sign up.

1-800-254-WALK (9255)
www.diabetes.org/walk

an event of American Diabetes Association®

AMERICA'S WALK FOR DIABETES

Don't be blind to diabetes.

* Dates may vary by market.

This ad is made possible through funding provided by the following corporations:

EQUAL. LUDEN'S People archway Estee HEALTH YAHOO! CHOICE

Feel Good At Snack Time

Introducing CHOICEdm® Nutrition Bar to help you manage your diabetes

Finally, there are peanutty chocolate and fudge brownie bars you can feel good about. Because they are good for you.

Unlike candy and energy bars which can result in high blood sugar levels, new CHOICE*dm* bars are made with a special slow-release carbohydrate, called resistant starch. Glucose is released more slowly, so blood sugar levels stay closer to normal.*

Designed with the American Diabetes Association Nutrition Recommendations in mind, CHOICE*dm* provides a convenient way to get complete nutrition, including 24 essential vitamins and minerals, with increased levels of the antioxidant vitamins. You feel good when your diabetes is in control. Try CHOICE*dm*!

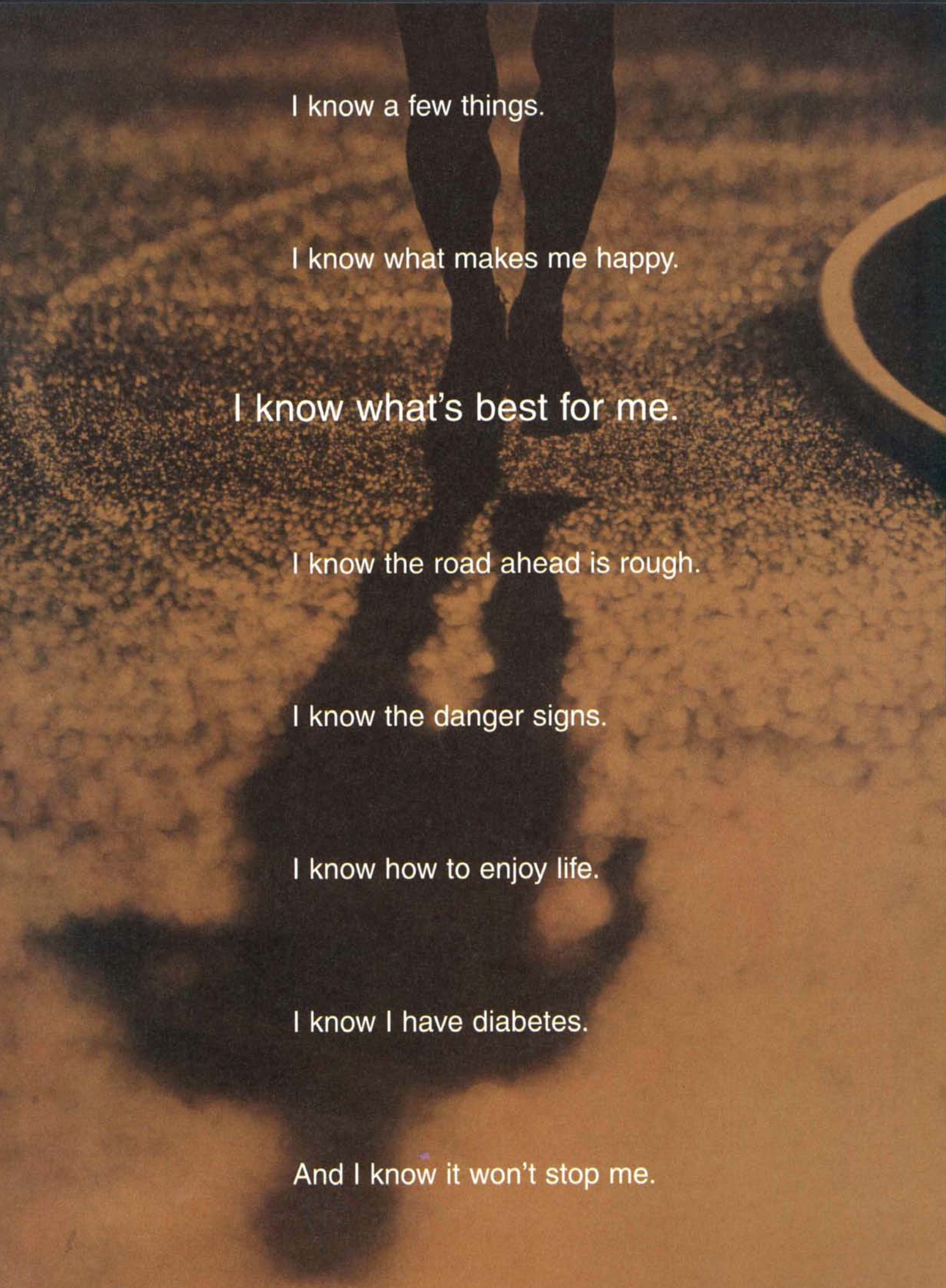
CHOICEdm®
For People With Diabetes

If not conveniently available in your area, call us at **1-800-247-7893.**
http://www.meadjohnson.com/choicedm

Mead Johnson™ Nutritionals

CHOICE*dm* is formulated to meet distinctive nutritional requirements for the dietary management of diabetes. See your health care professional regarding your specific dietary management plan.

* CHOICE*dm* results in a significantly lower increase in your blood glucose levels as compared to other snack bars tested. Source: Diabetes 1997; 46(1): 254A.


I know a few things.
I know what makes me happy.
I know what's best for me.
I know the road ahead is rough.
I know the danger signs.
I know how to enjoy life.
I know I have diabetes.
And I know it won't stop me.

The Accu-Chek family of products includes a blood glucose meter for every need.

Your patients may have accepted their diabetes, but they don't have to give in to it. That's why there's Accu-Chek. Whether it's our line of discreet, convenient products for monitoring their blood sugar, or our 24-hour Accu-Chek Customer Care℠ center to answer any questions, they can count on us to make living with their diabetes a little easier.

ACCU-CHEK™

Live life. We'll fit in.

Roche Diagnostics

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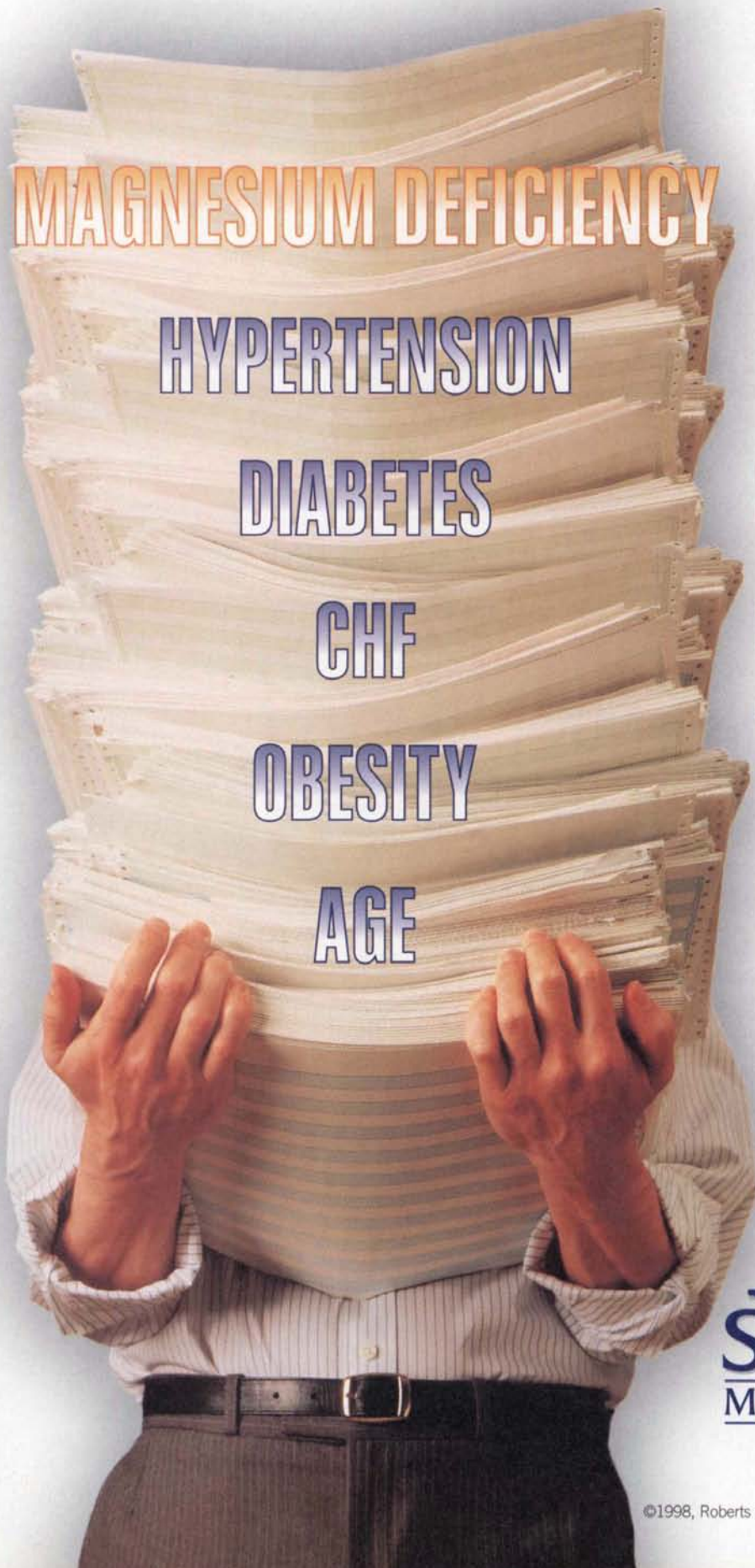
THE LAST STRAW?



Mg deficiency is common in disease states such as **hypertension**, **diabetes**, **cardiac arrhythmias**, and **congestive heart failure**. In hypomagnesemic patients at high risk, a recent consensus report advocates replenishing with oral magnesium chloride supplements of documented bioavailability and effectiveness.

ENTERIC-COATED SLOW-MAG® IS THE PREFERRED MAGNESIUM SUPPLEMENT

- Chloride formulation for high solubility
- Enteric coating for delayed-release in small intestine where Mg is more readily absorbed
- Minimal gastric upset
- Bioavailability unimpaired by low gastric acid
- Simple maintenance dosage enhances long-term compliance
- 2 tablets of SLOW-MAG daily provide 128 mg of elemental magnesium *plus* 220 mg of calcium carbonate

For additional information, samples and/or patient education brochures, call 1-800-828-2088

SLOW-MAG®
MAGNESIUM CHLORIDE

ROBERTS®

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

INSULIN-SPARING GLUCOSE CONTROL

ONCE-A-DAY

Amaryl®

glimepiride TABLETS

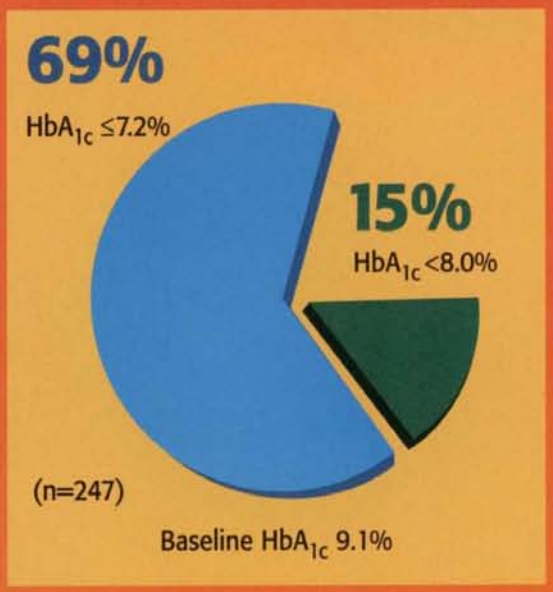
Please see brief summary of prescribing information on back.

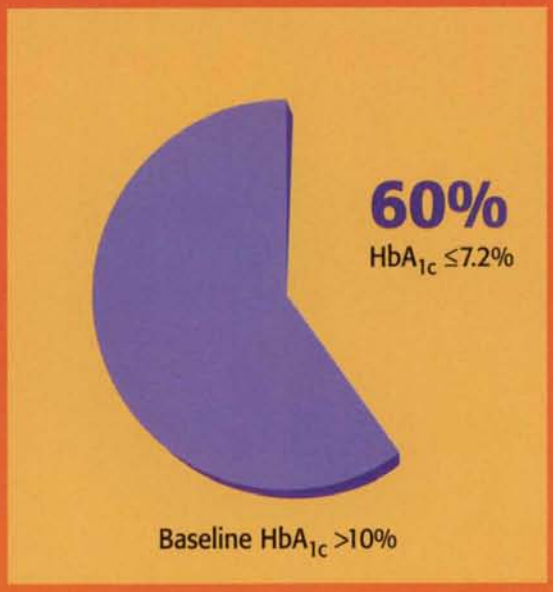
FEATURES LATEST CLINICAL RESULTS

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

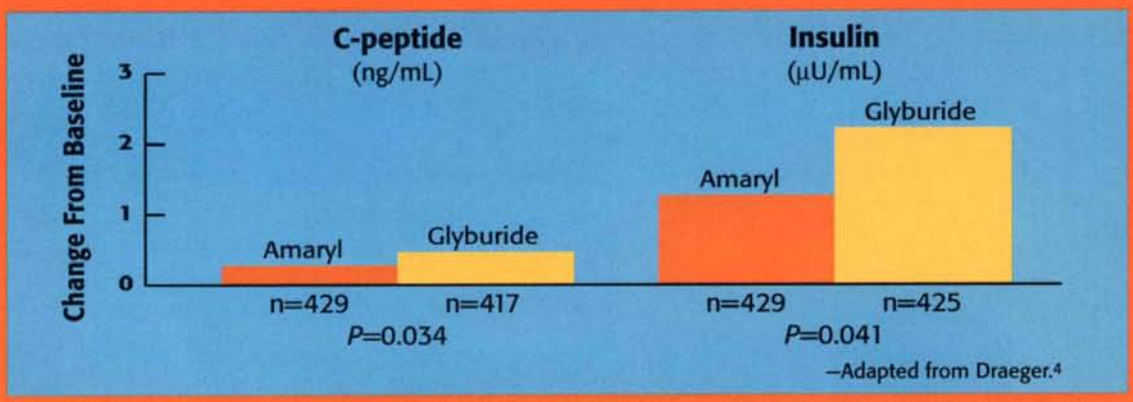
- 0.9% to 1.7% incidence of hypoglycemia as documented by blood glucose <60 mg/dL[2]
- Most common adverse reactions (>1%) include dizziness (1.7%), asthenia (1.6%), headache (1.5%), and nausea (1.1%)
- 60% renal, 40% hepatic dual route of elimination—100% biotransformed

*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 protonged 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

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97316101/2707R7

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

Hoechst

With the breakthrough oral medication for erectile dysfunction

VIAGRA®
(sildenafil citrate) tablets

INTRODUCING NEW
VIAGRA
THE SIMPLE NEW STEP TO IMPROVE ERECTILE FUNCTION

Now you can effectively treat erectile dysfunction (ED) with the ease of an oral medication

IMPROVES THE NATURAL SEXUAL RESPONSE

- VIAGRA relaxes the smooth muscle in the penis and allows erections to form the natural way—in response to sexual stimulation

THE EFFICACY YOUR PATIENTS WANT

- VIAGRA improved erections in up to 82% of patients
- VIAGRA resulted in successful intercourse in up to 66% of attempts
- VIAGRA is effective in a broad range of patients
- Efficacy was consistent regardless of baseline severity, etiology, race, and age (19 to 87 years)
- The vast majority of ED patients have mild to moderate ED. In general, VIAGRA patients who were less impaired at baseline responded best

NEW

VIAGRA™

(sildenafil citrate) tablets

The *simple step* to improve erectile function

Please see brief summary of prescribing information for VIAGRA (25-mg, 50-mg, 100-mg) tablets on last page.

VIAGRA
(sildenafil citrate) tablets

VIAGRA

THE BREAKTHROUGH ORAL MEDICATION FOR ERECTILE DYSFUNCTION

EFFECTIVELY IMPROVES ERECTIONS

Patients reported a significant improvement vs placebo in fixed-dose studies

VIAGRA	Placebo
up to 82%	24%

REMAINS EFFECTIVE OVER THE LONG TERM

IN A 1-YEAR, OPEN-LABEL STUDY:

Patients reporting improved erections

88%

EFFECTIVE IN A BROAD RANGE OF PATIENTS

VIAGRA improves erections in patients with...	VIAGRA	Placebo
Spinal cord injury	83%	12%
Depression	76%	18%
Hypertension	68%	18%
TURP	61%	34%
Diabetes	57%	10%
Radical prostatectomy	43%	15%

NEW

VIAGRA™

(sildenafil citrate) tablets

The *simple step* to improve erectile function

Please see brief summary of prescribing information for VIAGRA® (25-mg, 50-mg, 100-mg) tablets on last page.

VIAGRA
(sildenafil citrate) tablets

VIAGRA

THE MOST EXTENSIVELY STUDIED AND FIRST FDA-APPROVED ORAL TREATMENT FOR ERECTILE DYSFUNCTION

WELL TOLERATED: STUDIED IN MORE THAN 3000 PATIENTS

Discontinuation rate not different from placebo

VIAGRA	Placebo
2.5%	2.3%

The most common side effects are headache (16%), flushing (10%), and dyspepsia (7%).

CONTRAINDICATED IN PATIENTS USING ORGANIC NITRATES IN ANY FORM, AT ANY TIME

There is a degree of cardiac risk associated with sexual activity; therefore, physicians may wish to consider the cardiovascular status of their patients prior to initiating any treatment for ED.

Use of VIAGRA offers no protection against sexually transmitted diseases, including the human immunodeficiency virus (HIV); therefore, physicians may wish to consider counseling their patients about protective measures.

In clinical trials, mild and transient visual effects were reported (3%).

A SIGNIFICANT WINDOW OF OPPORTUNITY AFTER DOSING

VIAGRA may be taken anywhere from 4 hours to 1/2 hour before sexual activity. For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity. The maximum recommended dosing frequency is once per day.

WORKS FAST AND LASTS

NEW

VIAGRA™

(sildenafil citrate) tablets

The *simple step* to improve erectile function

Please see brief summary of prescribing information for VIAGRA (25-mg, 50-mg, 100-mg) tablets on last page.

THE SIMPLE NEW STEP TO IMPROVE ERECTILE FUNCTION

Brief summary of prescribing information

VIAGRA
(sildenafil citrate) tablets

INDICATION AND USAGE

VIAGRA is indicated for the treatment of erectile dysfunction. The studies that established benefit demonstrated improvements in success rates for sexual intercourse compared with placebo.

CONTRAINDICATIONS

Use of VIAGRA is contraindicated in patients with a known hypersensitivity to any component of the tablet. Consistent with its known effects on the nitric oxide/cGMP pathway (see CLINICAL PHARMACOLOGY), **VIAGRA was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are concurrently using organic nitrates in any form is therefore contraindicated.**

PRECAUTIONS

General

A thorough medical history and physical examination should be undertaken to diagnose erectile dysfunction, determine potential underlying causes, and identify appropriate treatment.

There is a degree of cardiac risk associated with sexual activity; therefore, physicians may wish to consider the cardiovascular status of their patients prior to initiating any treatment for erectile dysfunction.

Agents for the treatment of erectile dysfunction should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia).

The safety and efficacy of combinations of VIAGRA with other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

VIAGRA has no effect on bleeding time when taken alone or with aspirin. *In vitro* studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor). There is no safety information on the administration of VIAGRA to patients with bleeding disorders or active peptic ulceration. Therefore, VIAGRA should be administered with caution to these patients.

A minority of patients with the inherited condition retinitis pigmentosa have genetic disorders of retinal phosphodiesterases. There is no safety information on the administration of VIAGRA to patients with retinitis pigmentosa. Therefore, VIAGRA should be administered with caution to these patients.

Information for Patients

Physicians should discuss with patients the contraindication of VIAGRA with concurrent organic nitrates.

The use of VIAGRA offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including the Human Immunodeficiency Virus (HIV), may be considered.

Drug Interactions

Effects of Other Drugs on VIAGRA

***In vitro* studies:** Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance.

***In vivo* studies:** Cimetidine (800 mg), a non-specific CYP inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with VIAGRA (50 mg) to healthy volunteers.

When a single 100 mg dose of VIAGRA was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500 mg bid for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). Stronger CYP3A4 inhibitors such as ketoconazole, itraconazole or mibefradil would be expected to have still greater effects, and population data from patients in clinical trials did indicate a reduction in sildenafil clearance when it was co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, or cimetidine). It can be expected that concomitant administration of CYP3A4 inducers, such as rifampin, will decrease plasma levels of sildenafil.

Single doses of antacid (magnesium hydroxide/aluminum hydroxide) did not affect the bioavailability of VIAGRA.

Pharmacokinetic data from patients in clinical trials showed no effect on sildenafil pharmacokinetics of CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, ACE inhibitors, and calcium channel blockers. The AUC of the active metabolite, N-desmethyl sildenafil, was increased 62% by loop and potassium-sparing diuretics and 102% by non-specific beta-blockers. These effects on the metabolite are not expected to be of clinical consequence.

Effects of VIAGRA on Other Drugs

***In vitro* studies:** Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50 >150 μM). Given sildenafil peak plasma concentrations of approximately 1 μM after recommended doses, it is unlikely that VIAGRA will alter the clearance of substrates of these isoenzymes.

***In vivo* studies:** No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.

VIAGRA (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).

VIAGRA (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08%.

No interaction was seen when VIAGRA (100 mg) was co-administered with amlodipine in hypertensive patients. The mean additional reduction on supine blood pressure (systolic, 8 mmHg; diastolic, 7 mmHg) was of a similar magnitude to that seen when VIAGRA was administered alone to healthy volunteers (see CLINICAL PHARMACOLOGY).

Analysis of the safety database showed no difference in the side effect profile in patients taking VIAGRA with and without anti-hypertensive medication.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Sildenafil was not carcinogenic when administered to rats for 24 months at a dose resulting in total systemic drug exposure (AUCs) for unbound sildenafil and its major metabolite of 29- and 42-times, for male and female rats, respectively, the exposures observed in human males given the Maximum Recommended Human Dose (MRHD) of 100 mg. Sildenafil was not carcinogenic when administered to mice for 18-21 months at dosages up to the Maximum Tolerated Dose (MTD) of 10 mg/kg/day, approximately 0.6 times the MRHD on a mg/m² basis.

Sildenafil was negative in *in vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in vitro* human lymphocytes and *in vivo* mouse micronucleus assays to detect clastogenicity.

There was no impairment of fertility in rats given sildenafil up to 60 mg/kg/day for 36 days to females and 102 days to males, a dose producing an AUC value of more than 25 times the human male AUC.

There was no effect on sperm motility or morphology after single 100 mg oral doses of VIAGRA in healthy volunteers.

Pregnancy, Nursing Mothers and Pediatric Use

VIAGRA is not indicated for use in newborns, children, or women.

Pregnancy Category B. No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received up to 200 mg/kg/day during organogenesis. These doses represent, respectively, about 20 and 40 times the MRHD on a mg/m² basis in a 50 kg subject. In the rat pre- and postnatal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In non-pregnant rat the AUC at this dose was about 20 times human AUC. There are no adequate and well-controlled studies of sildenafil in pregnant women.

ADVERSE REACTIONS

VIAGRA was administered to over 3700 patients (aged 19-87 years) during clinical trials worldwide. Over 550 patients were treated for longer than one year.

In placebo-controlled clinical studies, the discontinuation rate due to adverse events for VIAGRA (2.5%) was not significantly different from placebo (2.3%). The adverse events were generally transient and mild to moderate in nature.

In trials of all designs, adverse events reported by patients receiving VIAGRA were generally similar. In fixed-dose studies, the incidence of some adverse events increased with dose. The nature of the adverse events in flexible-dose studies, which more closely reflect the recommended dosage regimen, was similar to that for fixed-dose studies.

When VIAGRA was taken as recommended (on an as-needed basis) in flexible-dose, placebo-controlled clinical trials the following adverse events were reported:

TABLE 1. ADVERSE EVENTS REPORTED BY ≥2% OF PATIENTS TREATED WITH VIAGRA AND MORE FREQUENT ON DRUG THAN PLACEBO IN PRN FLEXIBLE-DOSE PHASE II/III STUDIES

Adverse Event	Percentage of Patients Reporting Event	
	VIAGRA N=734	PLACEBO N=725
Headache	16%	4%
Flushing	10%	1%
Dyspepsia	7%	2%
Nasal Congestion	4%	2%
Urinary Tract Infection	3%	2%
Abnormal Vision[1]	3%	0%
Diarrhea	3%	1%
Dizziness	2%	1%
Rash	2%	1%

[1]Abnormal Vision: Mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision.

Other adverse reactions occurred at a rate of >2%,but equally common on placebo: respiratory tract infection, back pain, flu syndrome, and arthralgia.

In fixed-dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses. At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.

No cases of priapism were reported.

The following events occurred in < 2% of patients in controlled clinical trials; a causal relationship to VIAGRA is uncertain. Reported events include those with a plausible relation to drug use; omitted are minor events and reports too imprecise to be meaningful:

Body as a whole: face edema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury.

Cardiovascular: angina pectoris, AV block, migraine, syncope, tachycardia, palpitation, hypotension, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy.

Digestive: vomiting, glossitis, colitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, dry mouth, liver function tests abnormal, rectal hemorrhage, gingivitis.

Hemic and Lymphatic: anemia and leukopenia.

Metabolic and Nutritional: thirst, edema, gout, unstable diabetes, hyperglycemia, peripheral edema, hyperuricemia, hypoglycemic reaction, hypernatremia.

Musculoskeletal: arthritis, arthrosis, myalgia, tendon rupture, tenosynovitis, bone pain, myasthenia, synovitis.

Nervous: ataxia, hypertonia, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, reflexes decreased, hypesthesia.

Respiratory: asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.

Skin and appendages: urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.

Special senses: mydriasis, conjunctivitis, photophobia, tinnitus, eye pain, deafness, ear pain, eye hemorrhage, cataract, dry eyes.

Urogenital: cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema and anorgasmia.

OVERDOSAGE

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but incidence rates were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

HC150R98

NEW
VIAGRA
(sildenafil citrate) tablets

HC155A98

Pfizer U.S. Pharmaceuticals

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. **Endocrine Function** — HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine. **CNS Toxicity** — Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day. CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. **Carcinogenesis, Mutagenesis, Impairment of Fertility** — In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose. A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose. *In vitro*, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test. Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years. **Pregnancy: Pregnancy Category X — See CONTRAINDICATIONS.** Safety in pregnant women has not been established. Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2). In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. LIPITOR should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking LIPITOR, it should be discontinued and the patient advised again as to the potential hazards to the fetus. **Nursing Mothers:** Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see CONTRAINDICATIONS). **Pediatric Use:** Treatment experience in a pediatric population is limited to doses of LIPITOR up to 80 mg/day for 1 year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients. None of these patients was below 9 years of age. **Geriatric Use:** Treatment experience in adults age ≥70 years with doses of LIPITOR up to 80 mg/day has been evaluated in 221 patients. The safety and efficacy of LIPITOR in this population were similar to those of patients <70 years of age.

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

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

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

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

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

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

℞ **only**

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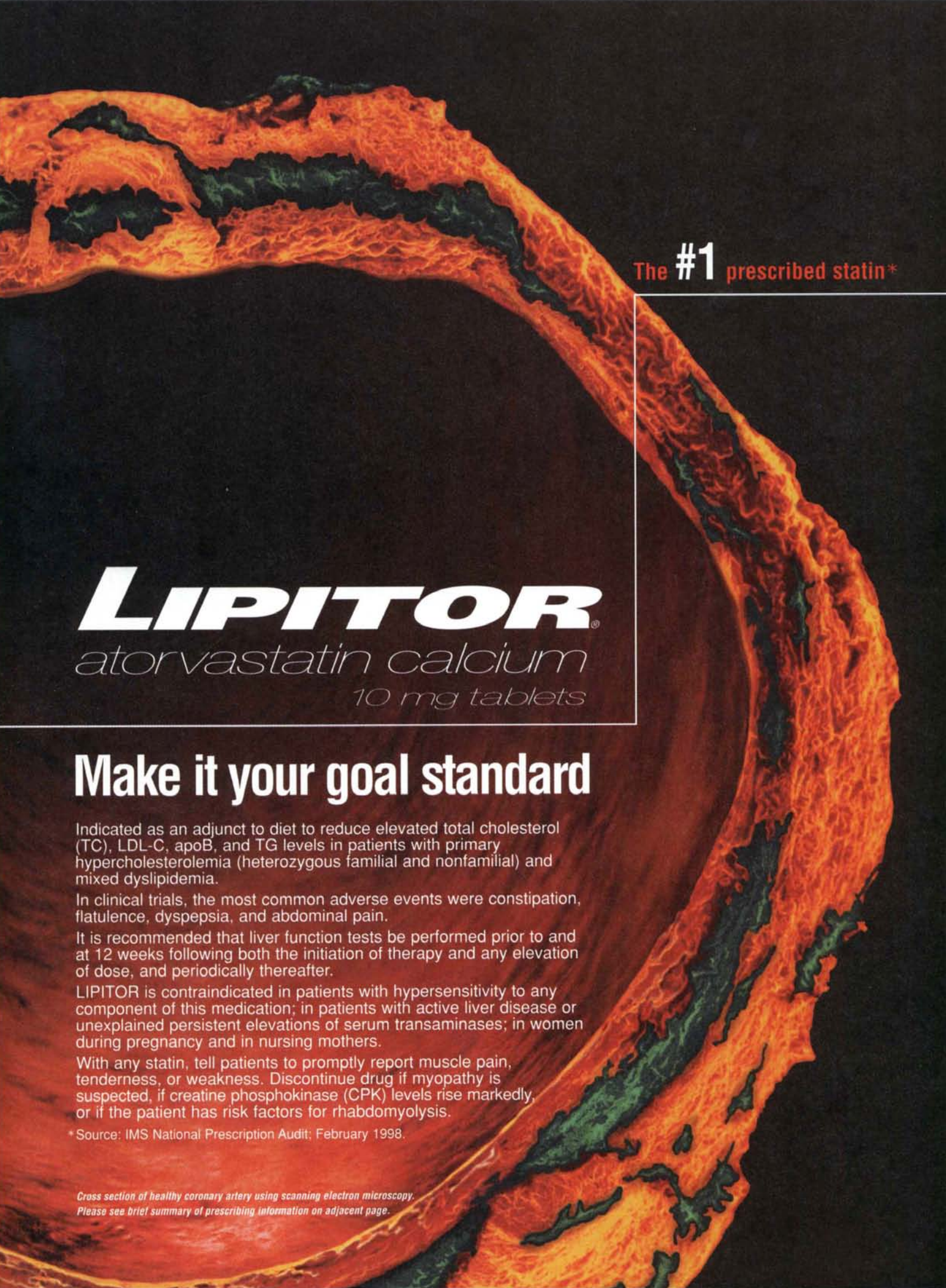
The #1 prescribed statin*
LIPITOR®
atorvastatin calcium
10 mg tablets
Make it your goal standard
Indicated as an adjunct to diet to reduce elevated total cholesterol (TC), LDL-C, apoB, and TG levels in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.
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.