THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

VOLUME 21 NUMBER 5

Diabetes Care

MAY 1998

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American Diabetes Association.

ISSN 0149-5992


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

they know how crucial diet and exercise are.

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

Choose it for **control.**

Choose it for **convenience.**

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GlucotrolXL®

(glipizide) extended release

Tablets 5 mg and 10 mg GITS®

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

Brief Summary of Prescribing Information

INDICATIONS AND USAGE: GLUCOTROL XL is indicated as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with non-insulin-dependent diabetes mellitus (NIDDM; type II), formerly known as maturity-onset diabetes, after an adequate trial of dietary therapy has proved unsatisfactory.

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

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

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

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

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

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Renal or hepatic insufficiency may affect the disposition of glipizide and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of Control of Blood Glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue glipizide and administer insulin.

Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

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

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

Patients should be informed of the potential risks and advantages of GLUCOTROL XL and of alternative modes of therapy. They should also be informed about the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose.

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

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. *In vitro* binding studies with human serum proteins indicate that glipizide binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to the clinical situation and in the use of glipizide with these drugs.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility: A twenty month study in rats and an eighteen month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. *Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.*

Pregnancy: Pregnancy Category C. Glipizide was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of glipizide. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well controlled studies in pregnant women. Glipizide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. If glipizide is used during pregnancy, it should be discontinued at least one month before the expected delivery date.

Nursing Mothers: Although it is not known whether glipizide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. A decision should be made whether to discontinue nursing or to discontinue the drug. If the drug is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

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

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

ADVERSE REACTIONS: In U.S. controlled studies the frequency of serious adverse experiences reported was very low and causal relationship has not been established.

The 580 patients from 31 to 87 years of age who received GLUCOTROL XL Extended Release Tablets in doses from 5 mg to 60 mg in both controlled and open trials were included in the evaluation of adverse experiences. All adverse experiences reported were tabulated independently of their possible causal relation to medication.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

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

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

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

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

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

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

Metabolic: Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas. In the mouse, glipizide pretreatment did not cause an accumulation of acetaldehyde after ethanol administration. Clinical experience to date has shown that glipizide has an extremely low incidence of disulfiram-like alcohol reactions.

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

OVERDOSAGE: Overdosage can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours since hypoglycemia may recur after apparent clinical recovery. Clearance of glipizide from plasma may be prolonged in persons with liver disease. Because of the extensive protein binding of glipizide, dialysis is unlikely to be of benefit.

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

In general, GLUCOTROL XL should be given with breakfast.

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

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

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

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

More detailed information available on request.

LC150R95 Revised Oct. 1995

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THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

VOLUME 21 NUMBER 5

Diabetes Care

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

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

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

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

Diabetes Care (ISSN 0149-5992) is published monthly by the American Diabetes Association, Inc., 1660 Duke Street, Alexandria, VA 22314. Individual subscription rates are $110 in the U.S., Canada, and Mexico (for Canada add 7% GST) and $170 for all other countries. Institutional rates are $180 in the U.S., Canada, and Mexico (for Canada add 7% GST) and $240 in all other countries. Professional membership includes $75 designated for *Diabetes Care*. Single issues are $13.50 in the U.S., Canada, and Mexico (Canada add 7% GST) and $17.00 in all other countries. Periodical postage paid at Alexandria, VA 22314, and at additional mailing offices. For more subscription information, call toll free (800) 232-3472, 8:30 A.M. to 8:00 P.M., E.T., Monday through Friday. Outside the U.S., call (703) 549-1500.

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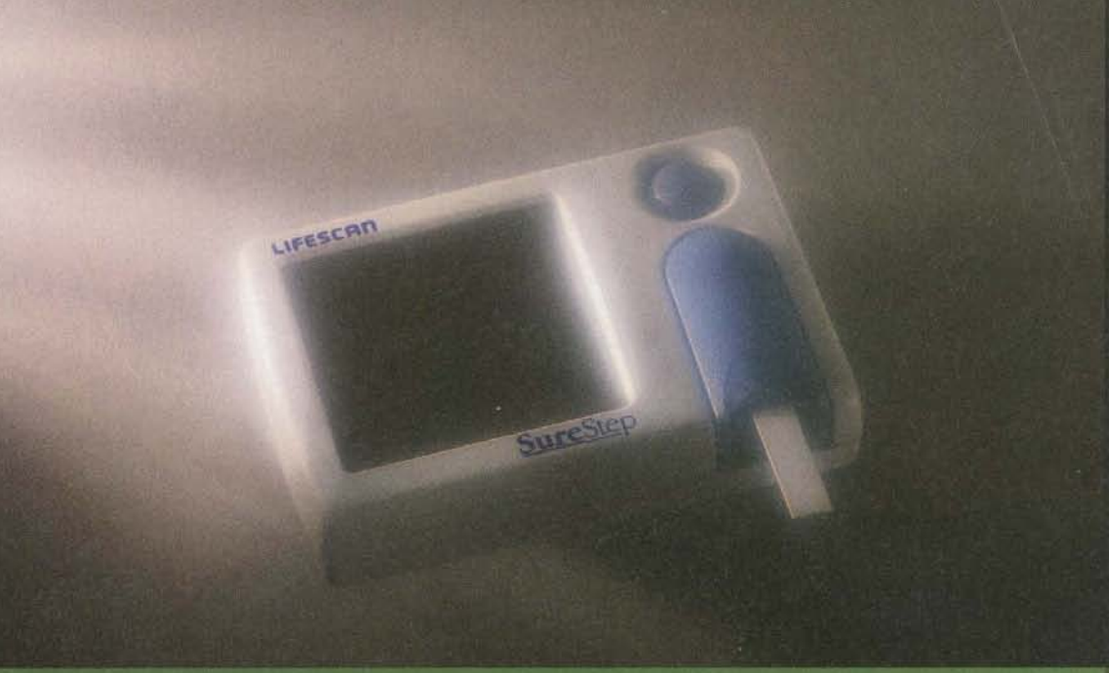
The mission of the American Diabetes Association is to prevent and cure diabetes and to improve the lives of all people affected by diabetes.

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



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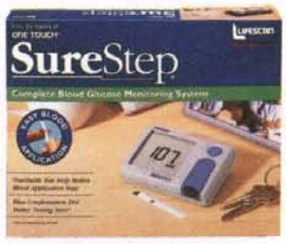

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Diabetes Care

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

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COVER: *The Boats at Luxembourg Garden* by Nanette Biers, 1993. Oil, 22" × 28".

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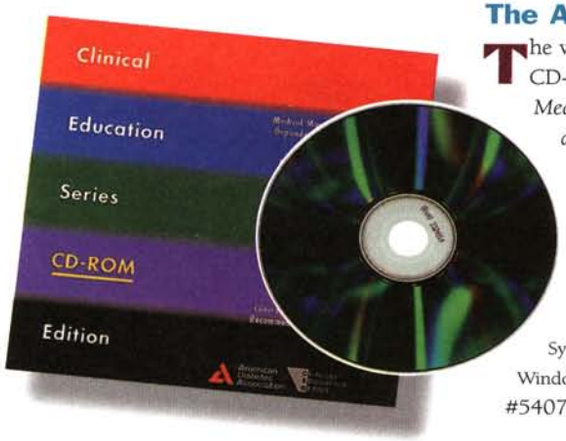

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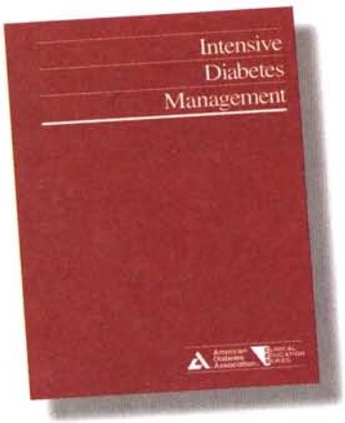

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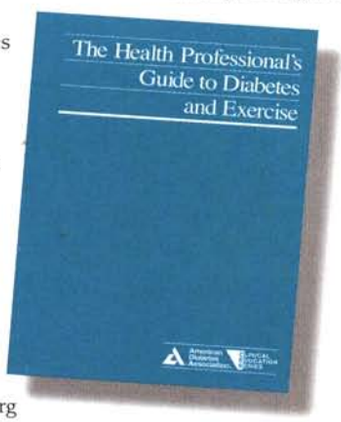

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* REGRANEX Gel is indicated for diabetic neuropathic foot ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. REGRANEX Gel is an adjunct to, and not a substitute for, good wound care, which includes initial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

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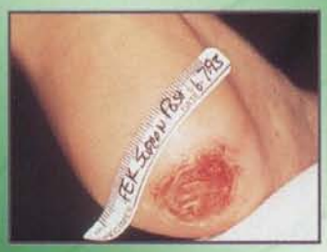
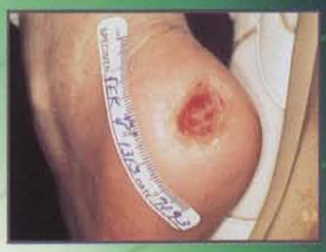
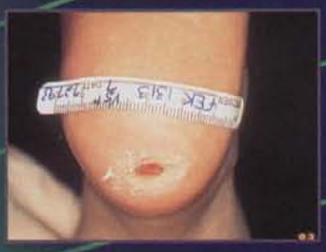


After debridement, prior to therapy with REGRANEX Gel



After 2 weeks of REGRANEX Gel plus good wound care



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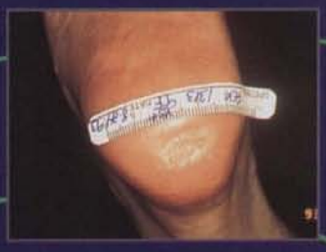

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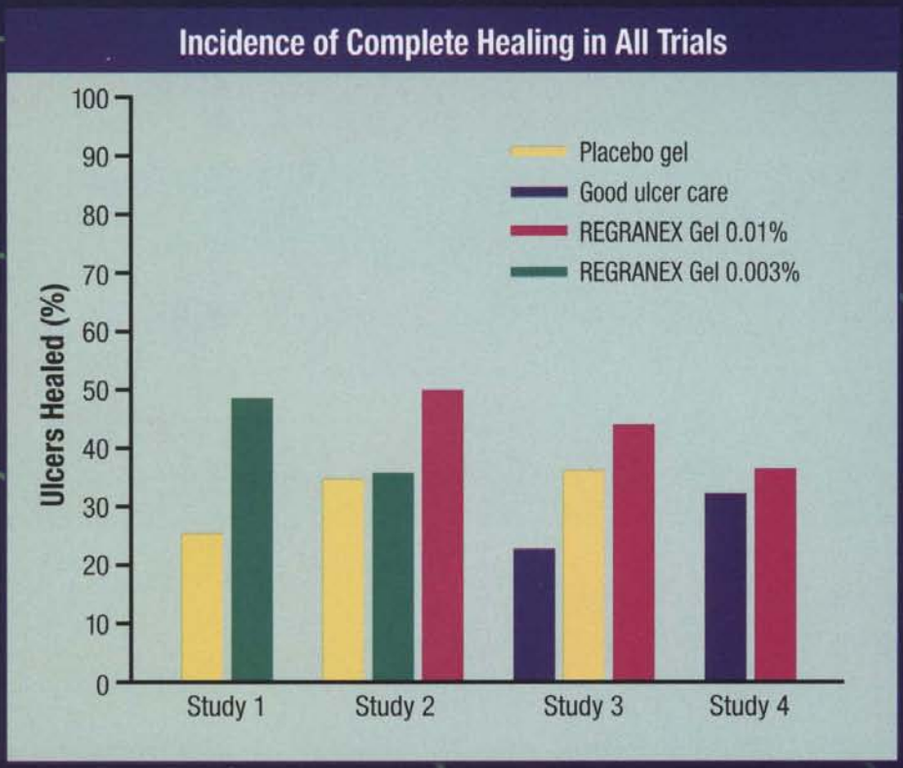
When combined with good wound care, REGRANEX Gel increased the incidence of complete healing



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

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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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Becaplermin Concentrate provided by: Chiron Corp.,
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 Revised February 1998 635-10-240-2B

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TRANSFORMING WOUND CARE TO WOUND HEALING

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 02J2881W 3/98

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

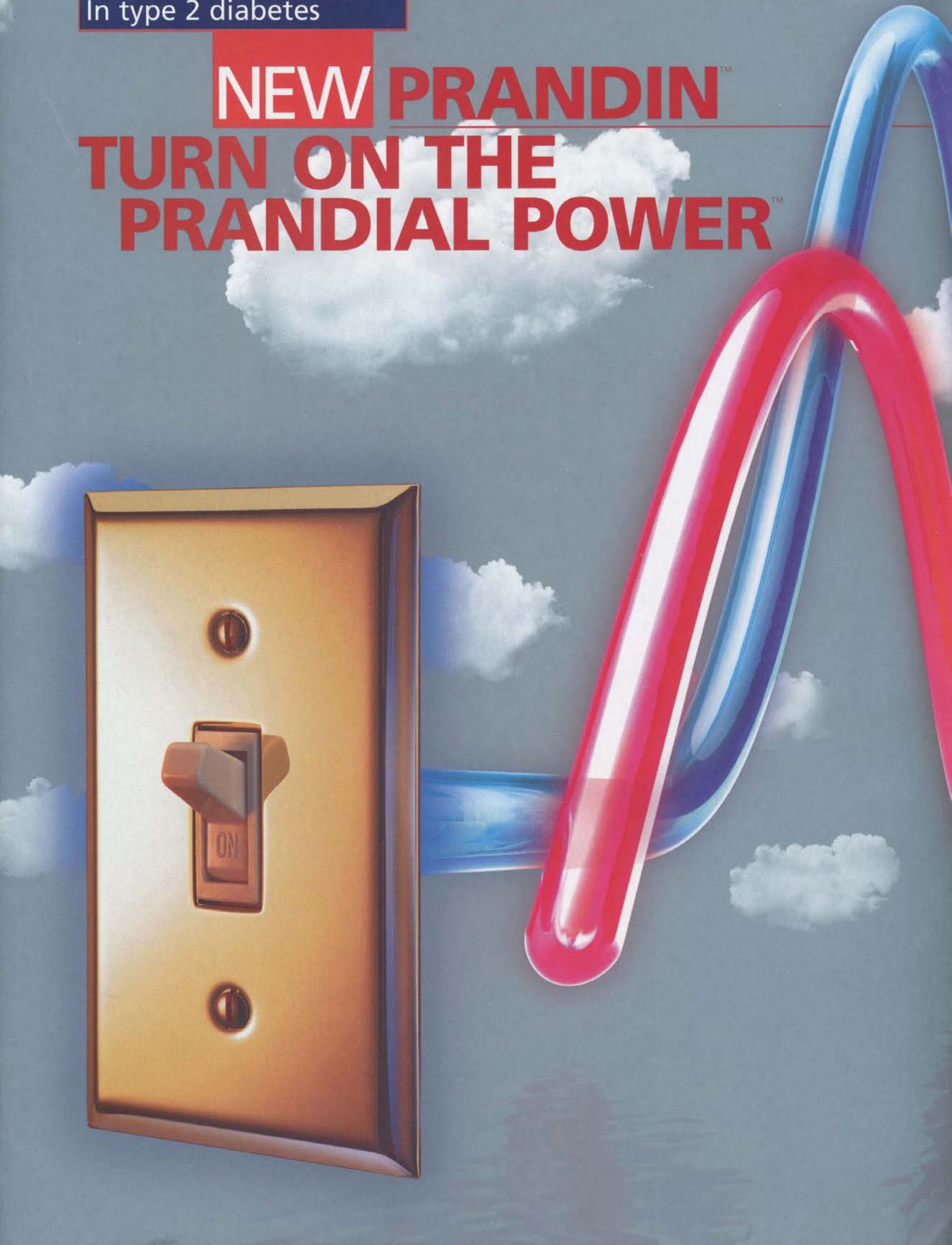
TURN ON THE PRANDIAL POWER™

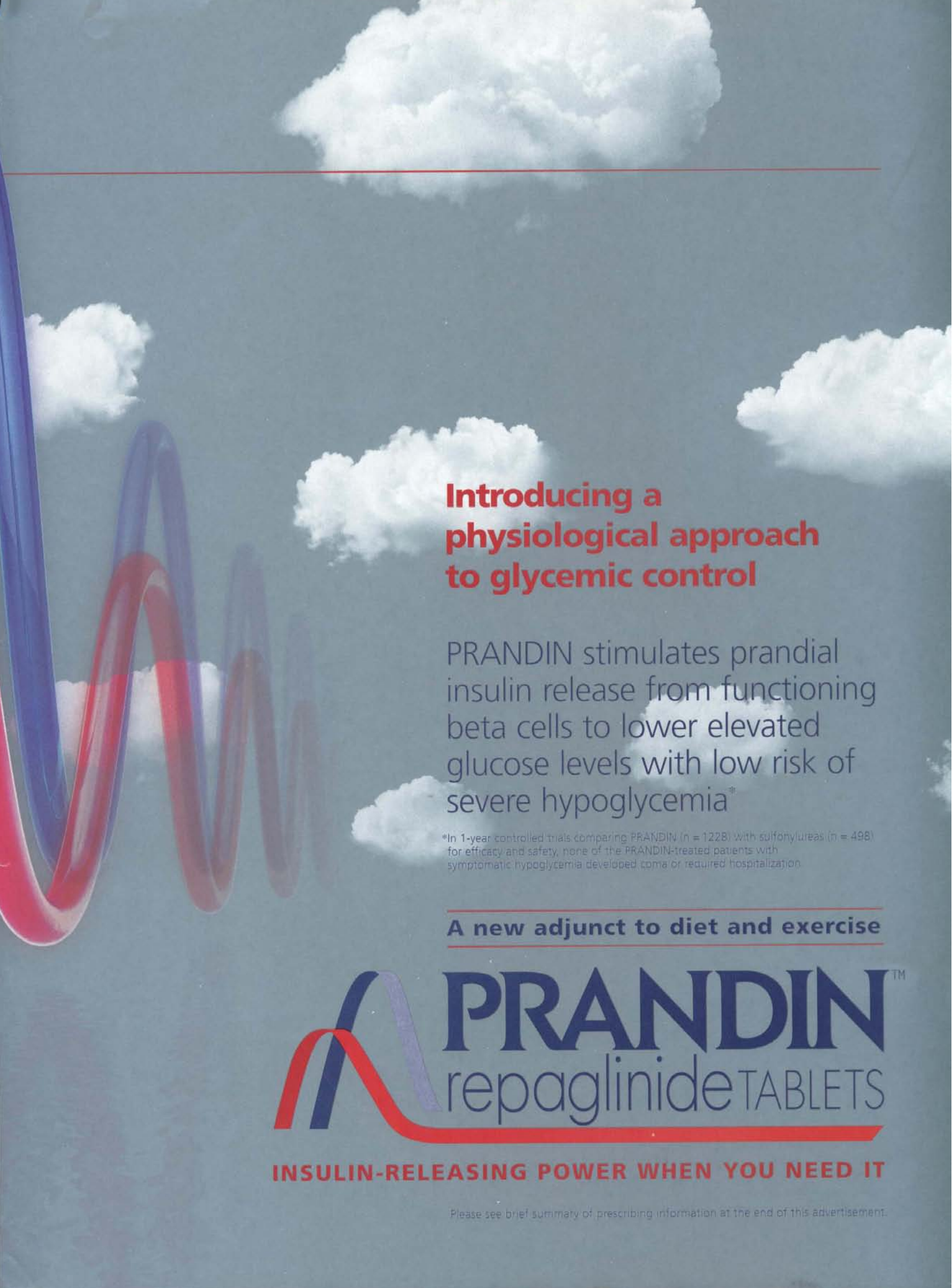
From Novo Nordisk, world leader in diabetes care

In type 2 diabetes

NEW PRANDIN™

TURN ON THE PRANDIAL POWER™





Introducing a physiological approach to glycemic control

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

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

A new adjunct to diet and exercise

PRANDIN™
repaglinide TABLETS

INSULIN-RELEASING POWER WHEN YOU NEED IT

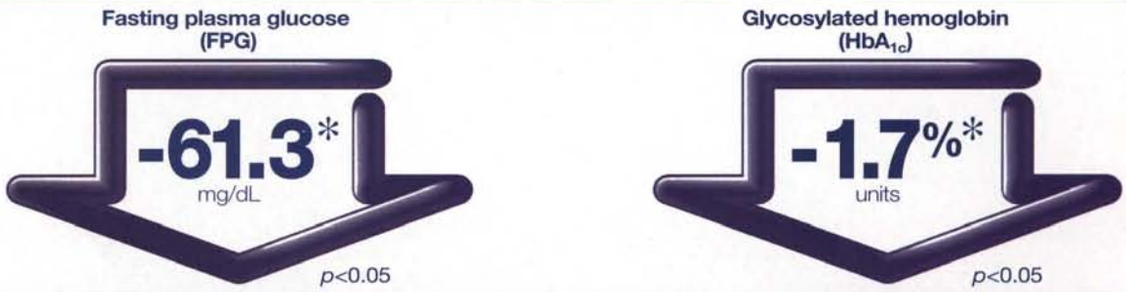
Please see brief summary of prescribing information at the end of this advertisement.

In type 2 diabetes

NEW PRANDIN™ TURN ON THE PRANDIAL POWER™

Effective first-line therapy

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

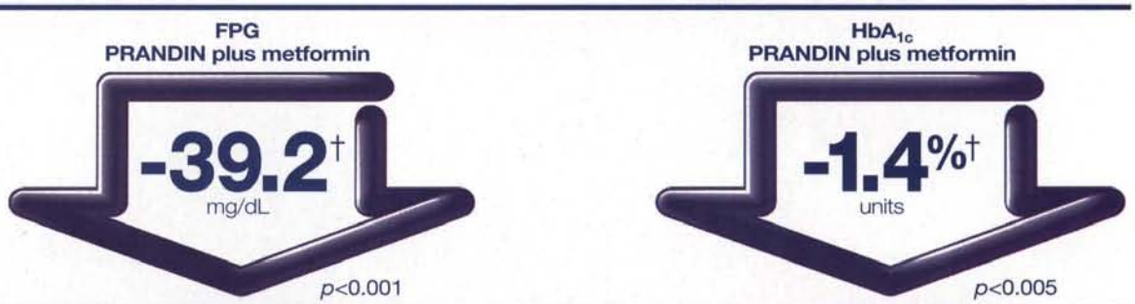


* Represents change between placebo and PRANDIN: FPG (placebo=30.3 mg/dL; PRANDIN=–31 mg/dL); HbA_{1c} (placebo=1.1% units; PRANDIN=–0.6% units).

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

Synergistic with metformin

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



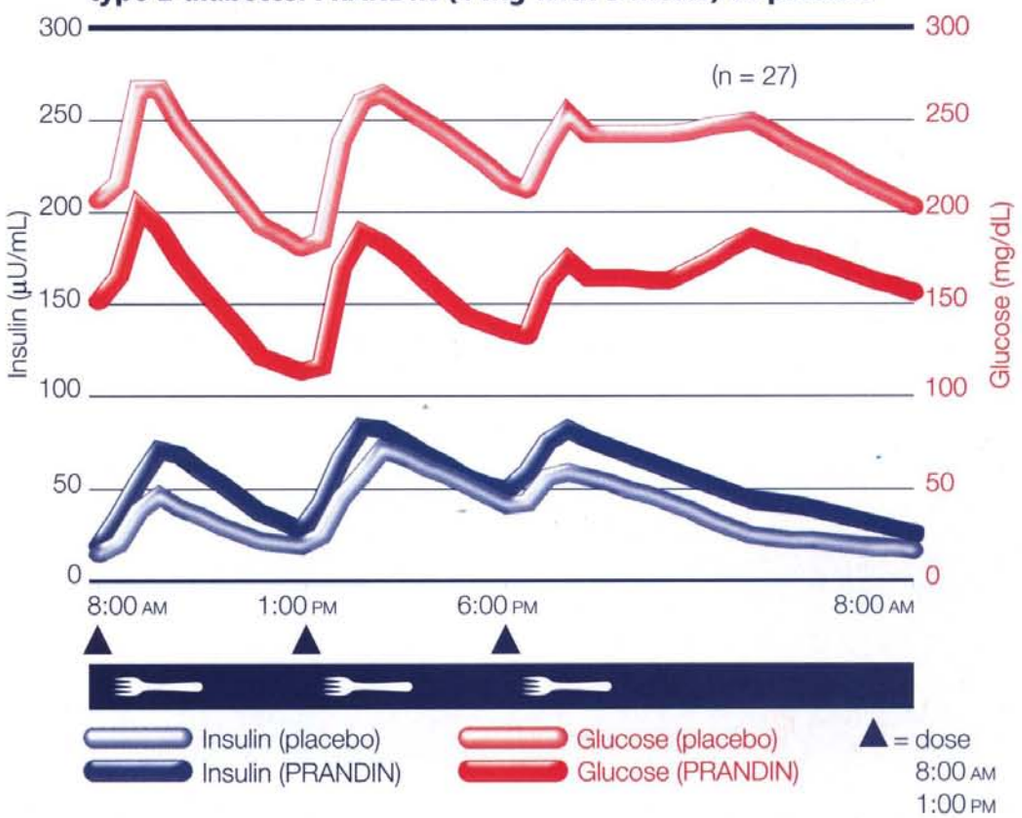
† Combination therapy change from baseline: metformin monotherapy: (FPG=–4.5 mg/dL; HbA_{1c}=–0.33% units); PRANDIN monotherapy: (FPG=8.8 mg/dL; HbA_{1c}=–0.38% units).

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

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

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

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



A new adjunct to diet and exercise

PRANDIN™
repaglinide TABLETS

INSULIN-RELEASING POWER WHEN YOU NEED IT

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

In type 2 diabetes

NEW PRANDIN™ TURN ON THE PRANDIAL POWER™

A well defined metabolic profile

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

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

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

Low rate of discontinuation due to hypoglycemia

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

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

Low risk of prolonged insulin stimulation

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

Important safety information

Commonly reported adverse events (% of patients)*

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

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

GI disturbance rate similar to placebo

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

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

A new adjunct to diet and exercise

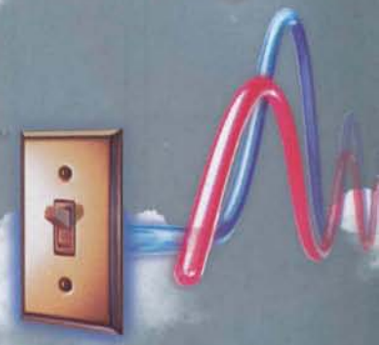
PRANDIN™
repaglinide TABLETS

INSULIN-RELEASING POWER WHEN YOU NEED IT

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

In type 2 diabetes

NEW PRANDIN™ TURN ON THE PRANDIAL POWER™



"Don't start a meal without it"

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

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

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

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

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

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

0.5 mg 1 mg 2 mg

A new adjunct to diet and exercise

PRANDIN™
repaglinide TABLETS

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

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

PRANDIN™ repaglinide TABLETS

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

BRIEF SUMMARY: CONSULT PACKAGE INSERT BEFORE PRESCRIBING PRANDIN.

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

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

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

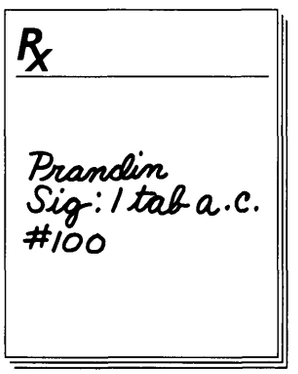
PRECAUTIONS Hypoglycemia: All oral blood glucose-lowering drugs are capable of producing hypoglycemia. Proper patient selection, dosage, and instructions to the patients are important to avoid hypoglycemic episodes. Hepatic insufficiency may cause elevated repaglinide blood levels and may diminish gluconeogenic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

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of glycemic control may occur. At such times, it may be necessary to discontinue PRANDIN and administer insulin.

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

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

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



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

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

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

Pregnancy: Pregnancy category C.

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

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

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

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

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

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

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

OVERDOSAGE In a clinical trial, patients received increasing doses of PRANDIN up to 80 mg a day for 14 days. There were few adverse effects other than those associated with the intended effect of lowering blood glucose. Hypoglycemia did not occur when meals were given with these high doses. Hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring may continue until the physician is assured that the patient is out of danger. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery. There is no evidence that repaglinide is dialyzable using hemodialysis. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL.

More detailed information is available on request.

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

PRANDIN is a trademark of Novo Nordisk A/S.

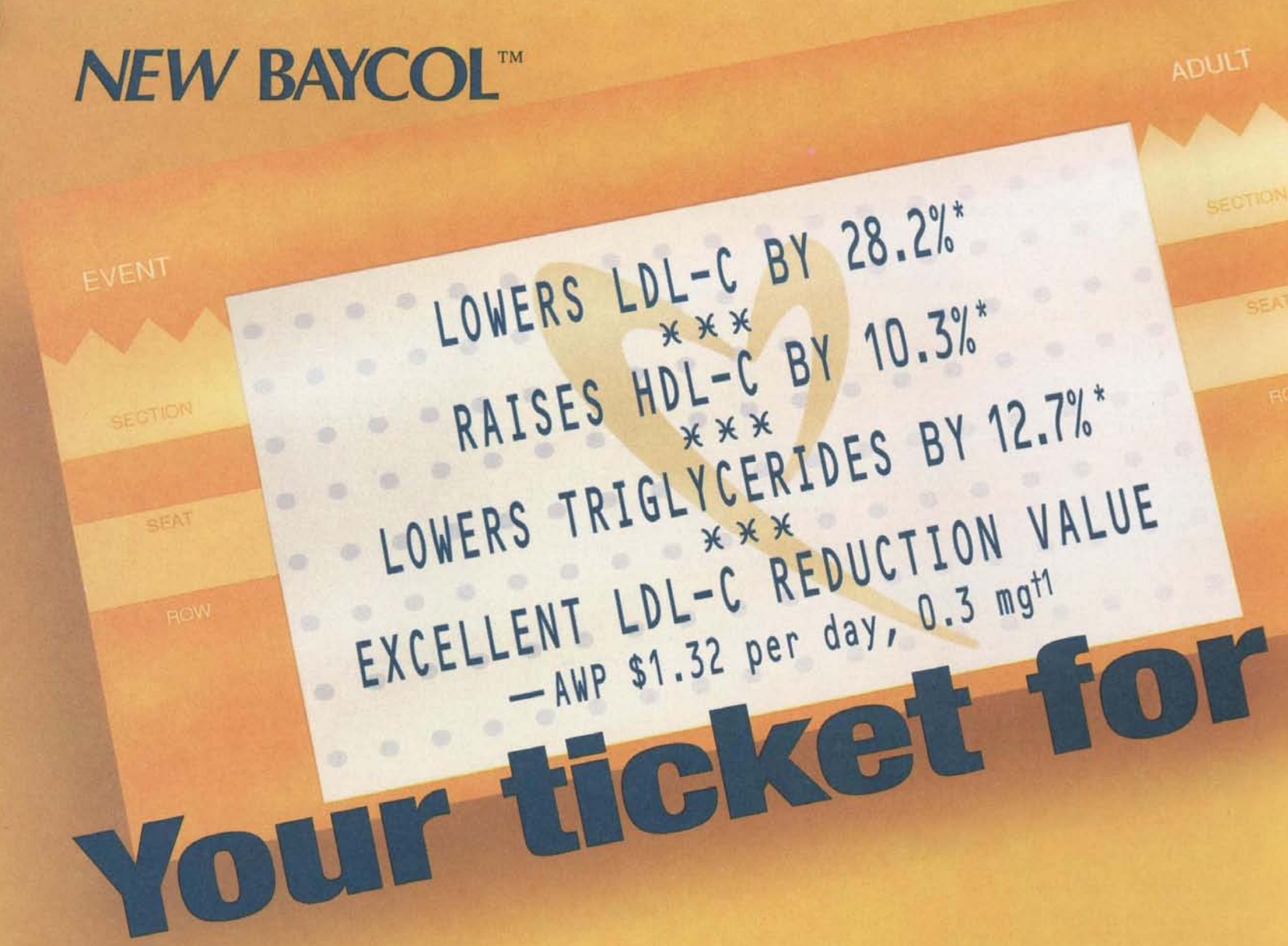
Novo Nordisk

Schering

123612

March 1998

NEW BAYCOL™



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

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

Important Safety Information

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

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

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

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

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

performance and value

NEW

Baycol™

cerivastatin sodium tablets

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

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

Bayer
Pharmaceutical Division

SB SmithKline Beecham Pharmaceuticals

BL6984 QO9037

Please see brief summary of prescribing information on next page.

BAYCOL™
(cerivastatin sodium tablets)

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

PZ500041BS 7/97

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

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

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

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

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

Table 2 National Cholesterol Education Program (NCEP) Treatment Guidelines

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

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

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

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

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

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

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

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

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

Hypersensitivity to any component of this medication.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Renal Insufficiency: Patients with significant renal impairment ($Cl_{cr} \leq 60$ mL/min/1.73m²) have increased AUC (up to 60%) and C_{max} (up to 23%) and should be administered BAYCOL™ with caution.

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

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

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

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

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

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

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

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

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

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

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

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

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

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

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

References:

1 Classification of Hyperlipoproteinemias

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

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

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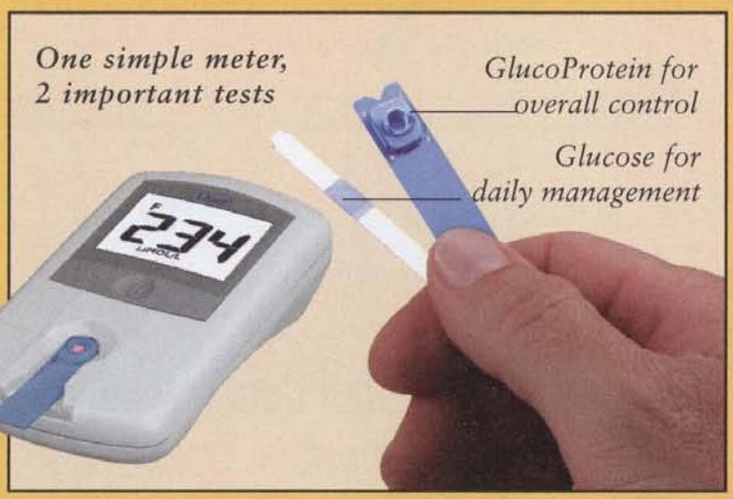

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Expansion of GENNID Project

The American Diabetes Association is expanding the reach of its GENNID Project, which is providing a carefully constructed DNA bank and database to foster identification of the genes responsible for type 2 diabetes. The Association is seeking new sites to recruit, phenotype, sample, and track siblings with type 2 diabetes.

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Further GENNID information can be found at www.diabetes.org/grants. For the complete RFA, please contact Matt Petersen, Director of Research Programs, Tel: (703) 299-2071, e-mail: mpetersen@diabetes.org

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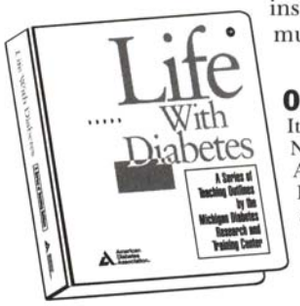

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Amaryl®

glimepiride TABLETS

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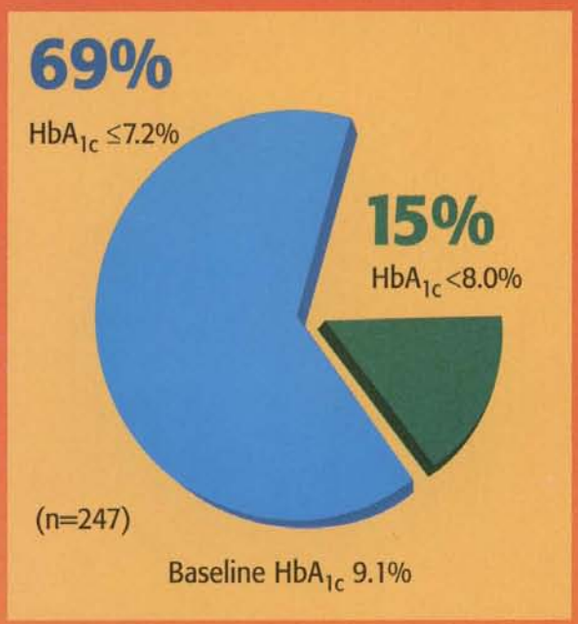

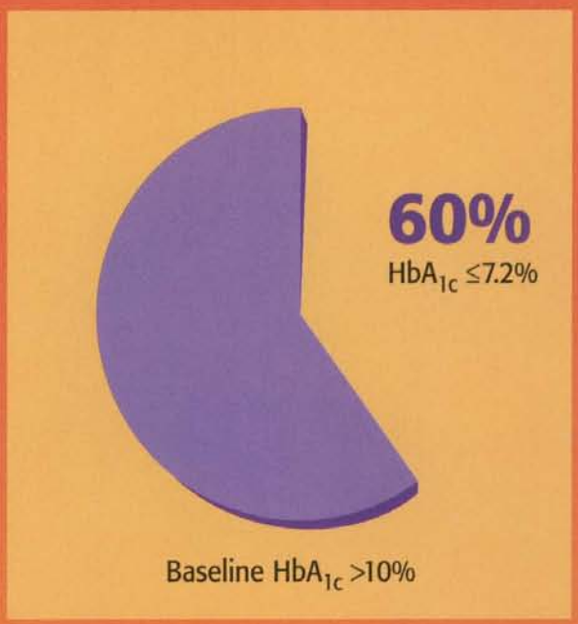

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- 0.9% to 1.7% incidence of hypoglycemia as documented by blood glucose <60 mg/dL[2]
- Most common adverse reactions (>1%) include dizziness (1.7%), asthenia (1.6%), headache (1.5%), and nausea (1.1%)
- 60% renal, 40% hepatic dual route of elimination—100%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

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

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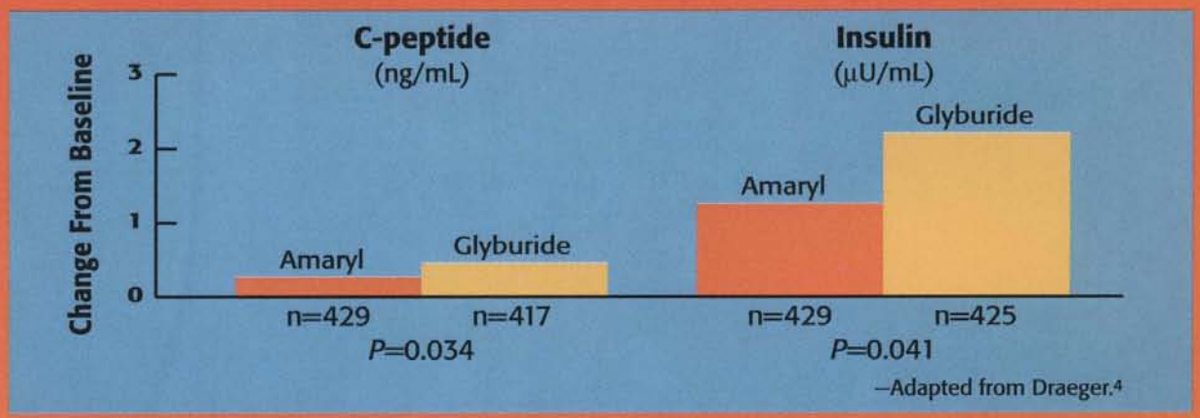
CLINICAL STUDIES DEMONSTRATE INSULIN-SPARING GLUCOSE CONTROL

- 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]

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

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Insulin-sparing glucose control

Brief Summary of
Prescribing Information as of November 1996

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1, 2, and 4 mg

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

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

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

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

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

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

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

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. Potential interactions of glimepiride with other drugs metabolized by cytochrome P450 II C9 also include phenytoin, diclofenac, ibuprofen, naproxen, and mefenamic acid.

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

INDICATIONS AND USAGE

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

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

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

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

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

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

CONTRAINDICATIONS

AMARYL® is contraindicated in patients with

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

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

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

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

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

PRECAUTIONS

General

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Patients with impaired renal function may be more sensitive to the glucose-lowering effect of AMARYL®. A starting dose of 1 mg once daily followed by appropriate dose titration is recommended in those patients. Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to add insulin in combination with AMARYL® or even use insulin monotherapy. The effectiveness of any oral hypoglycemic drug, including AMARYL®, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given. Should secondary failure occur with AMARYL® monotherapy, AMARYL®-insulin combination therapy may be instituted. Combined use of glimepiride and insulin may increase the potential for hypoglycemia.

Information for Patients

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

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

Laboratory Tests

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

Drug Interactions

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

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

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

Pregnancy

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

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

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

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. Patients who are planning a pregnancy should consult their physician, and it is recommended that they change over to insulin for the entire course of pregnancy and lactation.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

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

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

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

Adverse Events Occurring in ≥ 1% AMARYL® Patients

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

Gastrointestinal Reactions

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

Dermatologic Reactions

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

Hematologic Reactions

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

Metabolic Reactions

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

Other Reactions

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

Prescribing Information as of November 1996

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

US Patent 4,379,785

amab1196b

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

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

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Hoechst

Help protect patients at risk of First MI

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

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

First MI First MI First MI

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

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

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

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

*$p = 0.0001$

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

PRAVACHOL®
pravastatin sodium 20 mg tablets

Bristol-Myers Squibb Company

D3-K033C

Issued: March 1998

PRAVACHOL®
(pravastatin sodium) Tablets

Rx only

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

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

PRECAUTIONS: General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see **ADVERSE REACTIONS**). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin. *Homozygous Familial Hypercholesterolemia.* Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors. *Renal Insufficiency.* A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life ($t_{1/2}$) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored. **Information for Patients:** Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Drug Interactions:** *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See **WARNINGS: Skeletal Muscle.**

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

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

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

*Statistically significantly different from placebo.

In the Pravastatin Primary Prevention Study (West of Scotland Coronary Prevention Study) involving 6595 patients treated with PRAVACHOL (N=3302) or placebo (N=3293) for a median of 4.8 years and in the Cholesterol and Recurrent Events (CARE) study, involving 4159 men and women treated with PRAVACHOL (N=2081) or placebo (N=2078) for an average of 4.9 years the adverse event profile in the PRAVACHOL (pravastatin sodium) group was comparable to that of placebo for the duration of the studies. The following effects have been reported with drugs in this class; not all the effects listed below have necessarily been associated with pravastatin therapy: *Skeletal:* myopathy, rhabdomyolysis, arthralgia. *Neurological:* dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression. *Hypersensitivity Reactions:* An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. *Gastrointestinal:* pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting. *Skin:* alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported. *Reproductive:* gynecomastia, loss of libido, erectile dysfunction. *Eye:* progression of cataracts (lens opacities), ophthalmoplegia. *Laboratory Abnormalities:* elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities. **Laboratory Test Abnormalities:** Increases in serum transaminase (ALT, AST) values and CPK have been observed (see **WARNINGS**). Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with HMG-CoA reductase inhibitors. **Concomitant Therapy:** Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See **WARNINGS: Skeletal Muscle** and **PRECAUTIONS: Drug Interactions**.)

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

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Revised March 1998

I-32598

D3-B001-3-98

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Request for Applications:
Grants Available to Study Nutrition

The American Diabetes Association Research Program is seeking applications to study the nutritional aspects of diabetes

The American Diabetes Association Research Program is seeking applications to study the nutritional aspects of diabetes. Funding will be provided for two qualified projects. Applications studying the relationship between nutrition, particularly macronutrient intake, and the etiology, management, or treatment of diabetes will be considered. Possible topics of research interest include:

- Role of fat replacers in a healthy diet
- Most effective education/ counseling methods to encourage incorporation of healthy foods
- Optimal macronutrient components of a diet for people with diabetes
- Effect of the ratio of carbohydrate to fat intake on metabolic control, lipid profiles, and cardiovascular disease
- Diet and celiac disease in diabetes
- Effects of protein consumption on nephropathy and on glycemic control
- Appropriate meal plans for pregnant diabetic women

General Information

Clinical studies are encouraged, but human or animal studies are eligible. Applications must follow all American Diabetes Association Research Award guidelines and procedures, which are included with the application (see below). Investigators must be based in the United States and have citizenship or permanent resident status, be associated with an accredited research institution, and have a degree appropriate to the field of study.

Funding Information and Application Procedures

Grants will be made according to current ADA funding guidelines, which provide up to $75,000 of support per year for up to three years. The full RFA and application form can be obtained from the American Diabetes Association, Research Programs, 1660 Duke St., Alexandria, VA 22314, or by calling 703-549-1500, x. 2376. Budget stipulations are included in the application package. **Applications are due July 1, 1998.** For further information, please contact Matt Petersen, Director of Research Programs, at 703-299-2071, mpetersen@diabetes.org.

Review Criteria

Factors considered in evaluating applications include: scientific merit, including innovation, originality, and feasibility of the approach, adequacy of the experimental design, competence of the investigator to accomplish the research goals, and adequacy of the facilities. Up to two grants will be awarded depending on the merits and scope of the applications received.

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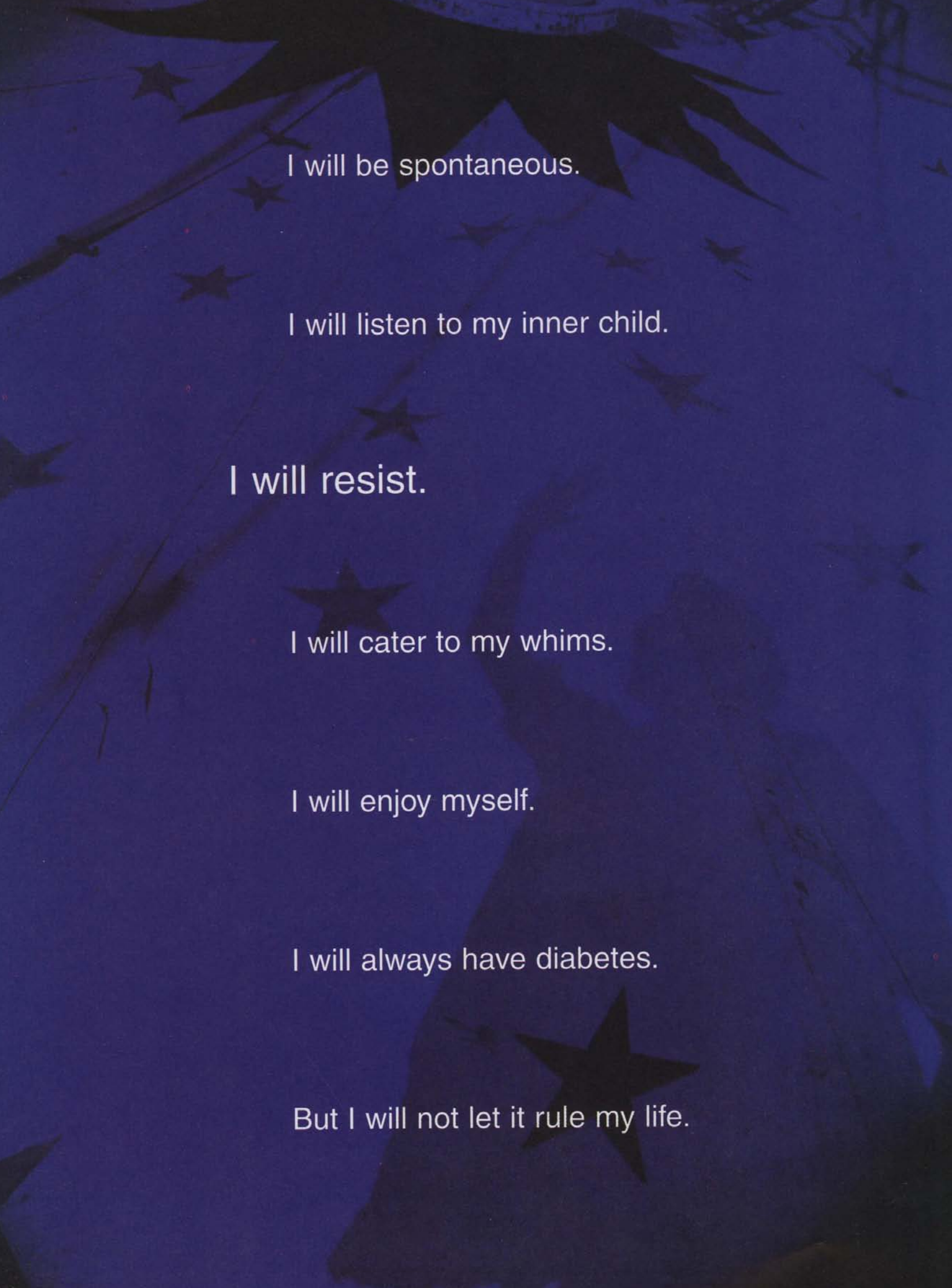

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Reference
1. Walker Information Study, 1997. Data on file, Eli Lilly and Company.

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Important Safety Information
Potential side effects associated with the use of all insulins, including Humalog, include hypoglycemia, weight gain, hypokalemia, lipodystrophy, and hypersensitivity. Because of the difference in action, care should be taken in patients in whom these conditions may be clinically relevant (e.g., those who have been fasting for a prolonged period, have autonomic neuropathy, or are using potassium-lowering drugs). **Starting or changing insulin therapy should be done cautiously and only under medical supervision.**

See accompanying brief summary for additional prescribing information.

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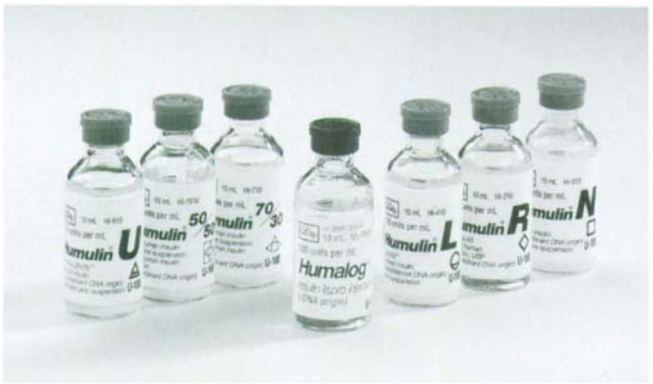

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1. Data on file. Eli Lilly and Company.

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Brief Summary: Please consult package insert for complete prescribing information.

INDICATIONS AND USAGE: Humalog is an insulin analog that is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. Humalog has a more rapid onset and a shorter duration of action than human regular insulin. Therefore, Humalog should be used in regimens including a longer-acting insulin.

CONTRAINDICATIONS: Humalog is contraindicated during episodes of hypoglycemia and in patients sensitive to Humalog or one of its excipients.

WARNINGS: This human insulin analog differs from human regular insulin by its rapid onset of action as well as a shorter duration of activity. When used as a mealtime insulin, the dose of Humalog should be given within 15 minutes before the meal. Because of the short duration of action of Humalog, patients with type I diabetes also require a longer-acting insulin to maintain glucose control.

Hypoglycemia is the most common adverse effect of insulins, including Humalog. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.[1]

PRECAUTIONS: *General*—Hypoglycemia, hypokalemia, lipodystrophy, and hypersensitivity are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of Humalog and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs).

As with all insulin preparations, the time course of Humalog action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during illness, emotional disturbances, or other stress.

Hypoglycemia—As with all insulin preparations, hypoglycemic reactions may be associated with the administration of Humalog. Rapid changes in serum glucose levels may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Renal and Hepatic Impairment—Although there are no specific data in patients with diabetes, Humalog requirements may be reduced in the presence of renal or hepatic impairment, similar to observations found with other insulins.

Allergy—Local Allergy—Patients occasionally experience redness, swelling, or itching at the site of injection. This condition, called local allergy, usually clears up in a few days to a few weeks. In some instances, this condition may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy—Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening. If patients think they are having such a reaction, they should notify a doctor immediately.

Antibody Production—In large clinical trials, antibodies that cross react with human insulin and insulin lispro were observed in both Humulin R- and Humalog-treatment groups. As expected, the largest increase in the antibody levels during the 12 month clinical trials was observed with patients new to insulin therapy.

Information for Patients—Patients should be informed of the potential risks and advantages of Humalog and alternative therapies. Patients should also be informed about the importance of proper insulin storage, injection technique, timing of dosage, adherence to meal planning, regular physical activity, regular blood glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, and periodic assessment for diabetes complications.

Patients should be advised to inform their physician if they are pregnant or intend to become pregnant.

Refer patients to the Information for the Patient circular for information on proper injection technique, timing of Humalog dosing (≤ 15 minutes before a meal), storing and mixing insulin, and common adverse effects.

Laboratory Tests—As with all insulins, the therapeutic response to Humalog should be monitored by periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control.

Drug Interactions—Insulin requirements may be increased by medications with hyperglycemic activity such as corticosteroids, isoniazid, certain lipid lowering drugs (e.g., niacin), estrogens, oral contraceptives, phenothiazines, and thyroid replacement therapy.

Insulin requirements may be decreased in the presence of drugs with hypoglycemic activity, such as oral hypoglycemic agents, salicylates, sulfa antibiotics, and certain antidepressants (monoamine oxidase inhibitors), certain angiotensin converting enzyme inhibitors, beta-adrenergic blockers, inhibitors of pancreatic function (e.g., octreotide), and alcohol. Beta-adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

Mixing of Insulins—Care should be taken when mixing all insulins as a change in peak action may occur. A decrease in the absorption rate, but not total bioavailability, was seen when Humalog was mixed with Humulin N. This decrease in absorption rate was not seen when Humalog was mixed with Humulin U. When Humalog is mixed with either Humulin U or Humulin N, the mixture should be given within 15 minutes before a meal.

If Humalog is mixed with a longer-acting insulin, Humalog should be drawn into the syringe first to prevent clouding of the Humalog by the longer-acting insulin. Injection should be made immediately after mixing. Mixtures should not be administered intravenously.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Humalog. Humalog was not mutagenic in a battery of *in vitro* and *in vivo* genetic toxicity assays (bacterial mutation tests, unscheduled DNA synthesis, mouse lymphoma assay, chromosomal aberration tests, and a micronucleus test). There is no evidence from animal studies of Humalog-induced impairment of fertility.

Pregnancy—Teratogenic Effects—Pregnancy Category B—

Reproduction studies have been performed in pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times, respectively, the average human dose (40 units/day) based on body surface area. The results have revealed no evidence of impaired fertility or harm to the fetus due to Humalog. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Although there are no clinical studies of the use of Humalog in pregnancy, published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome. Although the fetal complications of maternal hyperglycemia have been well documented, fetal toxicity also has been reported with maternal hypoglycemia. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

Nursing Mothers—It is unknown whether Humalog is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when Humalog is administered to a nursing woman. Patients with diabetes who are lactating may require adjustments in Humalog dose, meal plan, or both.

Pediatric Use—Safety and effectiveness in patients less than 12 years of age have not been established.

ADVERSE REACTIONS: Clinical studies comparing Humalog with human regular insulin did not demonstrate a difference in frequency of adverse events between the two treatments.

Adverse events commonly associated with human insulin therapy include the following:

Body as a Whole—allergic reactions (*see* PRECAUTIONS)
Skin and Appendages—injection site reaction, lipodystrophy, pruritus, rash
Other—hypoglycemia (*see* WARNINGS *and* PRECAUTIONS)

OVERDOSAGE: Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

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

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, analog), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

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1. American Diabetes Association: Clinical Practice Recommendations 1996, Insulin Administration. *Diabetes Care*, 1996; 19(Supp 1):31-34.

Literature revised July 30, 1997
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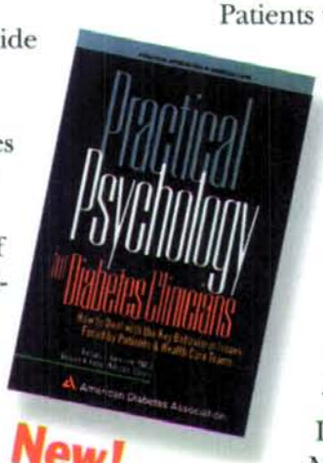

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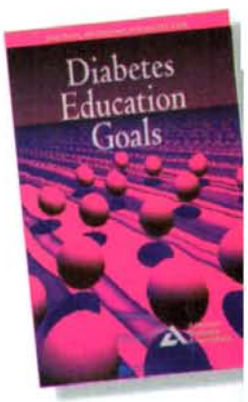

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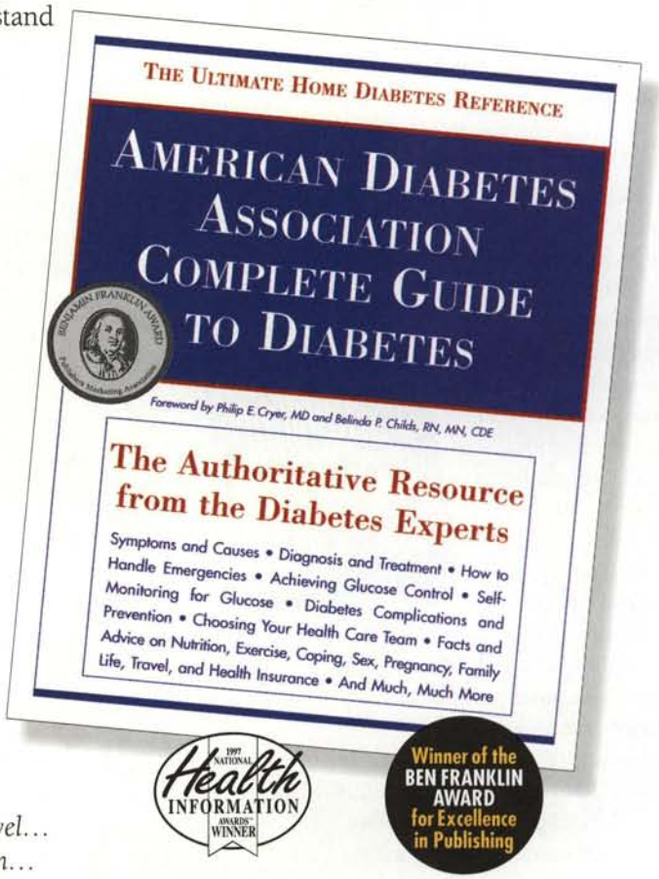

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ONCE-DAILY REZULIN® TROGLITAZONE TABLETS

WARNINGS
Hepatic
Rare cases of severe idiosyncratic hepatocellular injury have been reported during marketed use (see ADVERSE REACTIONS). The hepatic injury is usually reversible, but very rare cases of hepatic failure, leading to death or liver transplant, have been reported. Injury has occurred after both short- and long-term troglitazone treatment.
During all clinical studies in North America, a total of 48 of 2510 (1.9%) Rezulin-treated patients and 3 of 475 (0.6%) placebo-treated patients had ALT levels greater than 3 times the upper limit of normal. Twenty of the Rezulin-treated and one of the placebo-treated patients were withdrawn from treatment. Two of the 20 Rezulin-treated patients developed reversible jaundice; one of these patients had a liver biopsy which was consistent with an idiosyncratic drug reaction. An additional Rezulin-treated patient had a liver biopsy which was also consistent with an idiosyncratic drug reaction. (See ADVERSE REACTIONS, Laboratory Abnormalities.)
It is recommended that serum transaminase levels be checked at the start of therapy, monthly for the first six months of therapy, every two months for the remainder of the first year of troglitazone therapy, and periodically thereafter. Liver function tests also should be obtained for patients at the first symptoms suggestive of hepatic dysfunction, eg, nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine. Rezulin therapy should not be initiated if the patient exhibits clinical or laboratory evidence of active liver disease (eg, ALT>3 times the upper limit of normal) and should be discontinued if the patient has jaundice or laboratory measurements suggest liver injury (eg, ALT>3 times the upper limit of normal).

BRIEF SUMMARY
Consult Package Insert for full Prescribing Information.
INDICATIONS AND USAGE
Rezulin may be used concomitantly with a sulfonylurea or insulin to improve glycemic control. Rezulin, as monotherapy, is indicated as an adjunct to diet and exercise to lower blood glucose in patients with type II diabetes (see DOSAGE AND ADMINISTRATION in Package Insert for full Prescribing Information). Rezulin should not be used as monotherapy in patients previously well-controlled on sulfonylurea therapy. For patients inadequately controlled with a sulfonylurea alone, Rezulin should be added to, not substituted for, the sulfonylurea.
Management of type II diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient. This is important not only in the primary treatment of type II diabetes, but in maintaining the efficacy of drug therapy. Prior to initiation of Rezulin therapy, secondary causes of poor glycemic control, eg, infection or poor injection technique, should be investigated and treated.
CONTRAINDICATIONS
Rezulin is contraindicated in patients with known hypersensitivity or allergy to Rezulin or any of its components.
WARNINGS
SEE BOXED WARNING.
PRECAUTIONS
General
Because of its mechanism of action, Rezulin is active only in the presence of insulin. Therefore, Rezulin should not be used in type I diabetes or for the treatment of diabetic keto-acidosis.
Hypoglycemia: Patients receiving Rezulin in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia and a reduction in the dose of the concomitant agent may be necessary. Hypoglycemia has not been observed during the administration of Rezulin as monotherapy and would not be expected based on the mechanism of action.
Ovulation: In premenopausal anovulatory patients with insulin resistance, Rezulin treatment may result in resumption of ovulation. **These patients may be at risk for pregnancy.**
Hematologic: Across all clinical studies, hemoglobin declined by 3 to 4% in troglitazone-treated patients compared with 1 to 2% in those treated with placebo. White blood cell counts also declined slightly in troglitazone-treated patients compared to those treated with placebo. These changes occurred within the first four to eight weeks of therapy. Levels stabilized and remained unchanged for up to two years of continuing therapy. These changes may be due to the dilutional effects of increased plasma volume and have not been associated with any significant hematologic clinical effects (see ADVERSE REACTIONS, Laboratory Abnormalities).
Use in Patients With Heart Failure
Heart enlargement without microscopic changes has been observed in rodents at exposures of parent compound and active metabolite exceeding 7 times the AUC of the 400 mg human dose (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility, and Animal Toxicology). Serial echocardiographic evaluations in monkeys treated chronically at exposures at 4-9 times the human exposure to parent compound and active metabolite at the 400 mg dose did not reveal changes in heart size or function. In a 2-year echocardiographic clinical study using 600 to 800 mg/day of Rezulin in patients with type II diabetes, no increase in left ventricular mass or decrease in cardiac output was observed. The methodology employed was able to detect a change of about 10% or more in left ventricular mass.
In animal studies, troglitazone treatment was associated with increases of 6% to 15% in plasma volume. In a study of 24 normal volunteers, an increase in plasma volume of 6% to 8% compared to placebo was observed following 6 weeks of troglitazone treatment.
No increased incidence of adverse events potentially related to volume expansion (eg, congestive heart failure) have been observed during controlled clinical trials. However, patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during clinical trials. Therefore, Rezulin is not indicated unless the expected benefit is believed to outweigh the potential risk to patients with NYHA Class III or IV cardiac status.
Information for Patients
Rezulin should be taken with meals. If the dose is missed at the usual meal, it may be taken at the next meal. If the dose is missed on one day, the dose should not be doubled the following day.
It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. During periods of stress such as fever, trauma, infection, or surgery, insulin requirements may change and patients should seek the advice of their physician.
Patients who develop nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine or other symptoms suggestive of hepatic dysfunction or jaundice should immediately report these signs or symptoms to their physician.
When using combination therapy with insulin or oral hypoglycemic agents, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.
Use of Rezulin can cause resumption of ovulation in women taking oral contraceptives and in patients with polycystic ovary disease. Therefore, a higher dose of an oral contraceptive or an alternative method of contraception should be considered.
Rezulin may affect other medications used in diabetic patients. Patients started on Rezulin should ask their physician to review their other medications to make sure that they are not affected by Rezulin.
Drug Interactions
Oral Contraceptives: Administration of Rezulin with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%, which could result in loss of contraception. Therefore, a higher dose of oral contraceptive or an alternative method of contraception should be considered.
Terfenadine: Coadministration of Rezulin with terfenadine decreases the plasma concentration of both terfenadine and its active metabolite by 50-70% and may result in decreased efficacy of terfenadine.
Cholestyramine: Concomitant administration of cholestyramine with Rezulin reduces the absorption of troglitazone by 70%; thus, coadministration of cholestyramine and Rezulin is not recommended.
Glyburide: Coadministration of Rezulin and glyburide does not appear to alter troglitazone or glyburide pharmacokinetics.
Digoxin: Coadministration of Rezulin with digoxin does not alter the steady-state pharmacokinetics of digoxin.
Warfarin: Rezulin has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.
Acetaminophen: Coadministration of acetaminophen and Rezulin does not alter the pharmacokinetics of either drug.
Metformin: No information is available on the use of Rezulin with metformin.
Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in Rezulin-treated patients with type II diabetes mellitus.
The above interactions with terfenadine and oral contraceptives suggest that troglitazone may induce drug metabolism by CYP3A4. Studies have not been performed with other drugs metabolized by this enzyme such as: astemizole, calcium channel blockers, cisapride, corticosteroids, cyclosporine, HMG-CoA reductase inhibitors, tacrolimus, triazolam, and trimetrexate. The possibility of altered safety and efficacy should be considered when Rezulin is used concomitantly with these drugs.
Patients stable on one or more of these agents when Rezulin is started should be closely monitored and their therapy adjusted as necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Troglitazone was administered daily for 104 weeks to male rats at 100, 400, or 800 mg/kg and to female rats at 25, 50, or 200 mg/kg. No tumors of any type were increased at the low and mid doses. Plasma drug exposure based on AUC of parent compound and total metabolites at the low and mid doses was up to 24-fold higher than human exposure at 400 mg daily. The highest dose in each sex exceeded the maximum tolerated dose. In a 104-week study in mice given 50, 400, or 800 mg/kg, incidence of hemangiosarcoma was increased in females at 400 mg/kg and in both sexes at 800 mg/kg; incidence of hepatocellular carcinoma was increased in females at 800 mg/kg. The lowest dose associated with increased tumor incidence (400 mg/kg) was associated with AUC values of parent compound and total metabolites that were at least 2-fold higher than the human exposure at 400 mg daily. No tumors of any type were increased in mice at 50 mg/kg at exposures up to 40% of that in humans at 400 mg daily, based on AUC of parent compound and total metabolites.
Troglitazone was neither mutagenic in bacteria nor clastogenic in bone marrow of mice. Equivocal increases in chromosome aberrations were observed in an *in vitro* Chinese hamster lung cell assay. In mouse lymphoma cell gene mutations assays, results were equivocal when conducted with a microtiter technique and negative with an agar plate technique. A liver unscheduled DNA synthesis assay in rats was negative.
No adverse effects on fertility or reproduction were observed in male or female rats given 40, 200, or 1000 mg/kg daily prior to and throughout mating and gestation. AUC of parent compound at these doses was estimated to be 3- to 9-fold higher than the human exposure.
Animal Toxicology
Increased heart weights without microscopic changes were observed in mice and rats treated for up to 1 year at exposure (AUC) of parent and active metabolite exceeding 7 times the human AUC at 400 mg/day. These heart weight increases were reversible in 2- and 13-week studies, were prevented by coadministration of an ACE inhibitor, and 14 days of troglitazone administration to rats did not affect left ventricular performance. In the lifetime carcinogenicity studies, microscopic changes were noted in the hearts of rats but not in mice. In control and treated rats, microscopic changes included myocardial inflammation and fibrosis and karyomegaly of atrial myocytes. The incidence of these changes in drug-treated rats was increased compared to controls at twice the AUC of the 400 mg human dose.
Pregnancy
Pregnancy Category B. Troglitazone was not teratogenic in rats given up to 2000 mg/kg or rabbits given up to 1000 mg/kg during organogenesis. Compared to human exposure of 400 mg daily, estimated exposures in rats (parent compound) and rabbits (parent compound and active metabolite) based on AUC at these doses were up to 9-fold and 3-fold higher, respectively. Body weights of fetuses and offspring of rats given 2000 mg/kg during gestation were decreased. Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats given 40, 200, or 1000 mg/kg during late gestation and lactation periods; no effects were observed in offspring of rats given 10 or 20 mg/kg.
There are no adequate and well-controlled studies in pregnant women. Rezulin should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.
Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.
Nursing Mothers
It is not known whether troglitazone is secreted in human milk. Troglitazone is secreted in the milk of lactating rats. Because many drugs are excreted in human milk, Rezulin should not be administered to a breast-feeding woman.
Pediatric Use
Safety and effectiveness in pediatric patients have not been established.
Geriatric Use
Twenty-two percent of patients in clinical trials of Rezulin were 65 and over. No differences in effectiveness and safety were observed between these patients and younger patients.
ADVERSE REACTIONS
Two patients in the clinical studies developed reversible jaundice; one of these patients had a liver biopsy which was consistent with an idiosyncratic drug reaction. An additional patient had a liver biopsy which was also consistent with an idiosyncratic drug reaction. Symptoms that are associated with hepatic dysfunction have been reported, including: nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine, abnormal liver function tests (including increased ALT, AST, LDH, alkaline phosphatase, bilirubin). Also see WARNINGS.
The overall incidence and types of adverse reactions reported in placebo-controlled clinical trials for Rezulin-treated patients and placebo-treated patients are shown in Table 1. In patients treated with Rezulin in glyburide-controlled studies (N=550) or uncontrolled studies (N=510), the safety profile of Rezulin appeared similar to that displayed in Table 1. The incidence of withdrawals during clinical trials was similar for patients treated with placebo or Rezulin (4%).

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

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

Types of adverse events seen when Rezulin was used concomitantly with insulin (N=543) were similar to those during Rezulin monotherapy (N=1731), although hypoglycemia occurred on insulin combination therapy (see PRECAUTIONS).
Laboratory Abnormalities
Hematologic: Small decreases in hemoglobin, hematocrit, and neutrophil counts (within the normal range) were more common in Rezulin-treated than placebo-treated patients and may be related to increased plasma volume observed with Rezulin treatment. Hemoglobin decreases to below the normal range occurred in 5% of Rezulin-treated and 4% of placebo-treated patients.
Lipids: Small changes in serum lipids have been observed (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects in Package Insert for full Prescribing Information).
Serum Transaminase Levels: During all clinical studies in North America, a total of 48 of 2510 (1.9%) Rezulin-treated patients and 3 of 475 (0.6%) placebo-treated patients had ALT levels greater than 3 times the upper limit of normal. During controlled clinical trials, 2.2% of Rezulin-treated patients had reversible elevations in AST or ALT greater than 3 times the upper limit of normal, compared with 0.6% of patients receiving placebo. Hyperbilirubinemia (>1.25 upper limit of normal) was found in 0.7% of Rezulin-treated patients compared with 1.7% of patients receiving placebo. In the population of patients treated with Rezulin, mean and median values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline, while values for LDH were increased slightly (see WARNINGS).
Postintroduction Reports
Adverse events associated with Rezulin that have been reported since market introduction, that are not listed above, and for which causal relationship to drug has not been established include the following: congestive heart failure, weight gain, edema, fever, abnormal lab tests including increased CPK and creatinine, hyperglycemia, syncope, anemia, malaise.
Caution: Federal law prohibits dispensing without prescription.

December 1997

Manufactured by:
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Vega Baja, PR 00694
For:
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IN TYPE 2 DIABETES

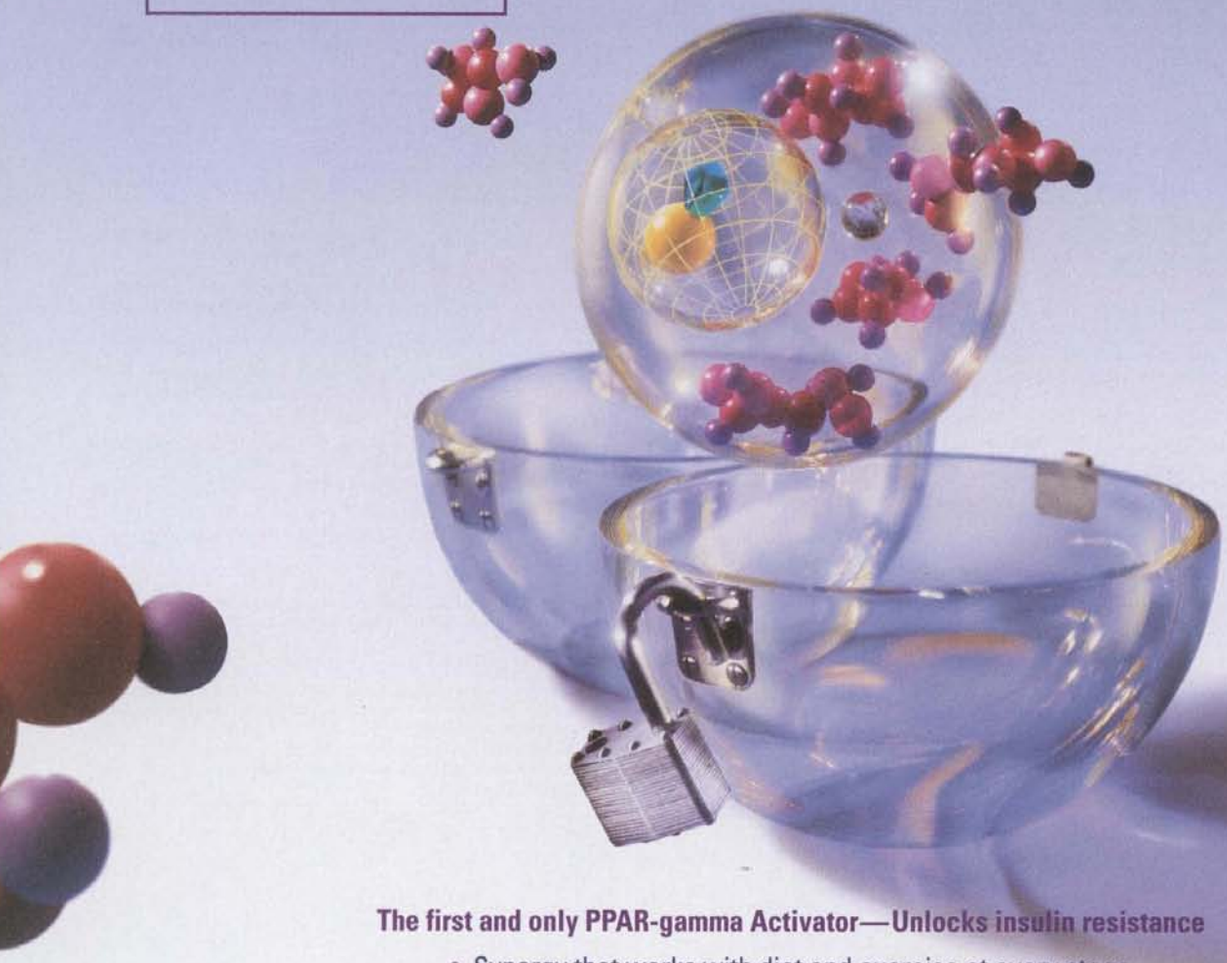
ONCE-DAILY

REZULIN®

TROGLITAZONE

200, 300, AND 400 MG TABLETS

New synergy in combination with sulfonylureas



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

- Synergy that works with diet and exercise at every stage
- Indicated for concomitant use with a sulfonylurea or insulin or as monotherapy, as an adjunct to diet and exercise, in type 2 diabetes

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

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

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

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

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

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

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

PD-168-JA-2009-E2(127)
710049

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