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Diabetes Care

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Original Articles

▶ *Table of contents continued*

American Diabetes Association®

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Today's hypertensives with new concerns...

THE CARDURA GENERATION

Choose CARDURA: first-line therapy for a new generation of hypertensives.

Choose CARDURA for around-the-clock blood pressure control that doesn't jeopardize blood lipids or blood sugar.[1-3]

CARDURA is well tolerated. In placebo-controlled studies, only three common side effects were reported significantly more often than with placebo: dizziness, somnolence, and fatigue. These were generally mild and transient. Only 2% of patients discontinued therapy due to adverse effects— the same as with placebo. Syncope has been reported, but rarely (<1%).

ONCE-A-DAY

CARDURA®

(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

HYPERTENSION CONTROL FOR A NEW GENERATION.

Please see brief summary of prescribing information on next page.

ONCE-A-DAY

CARDURA®

(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

References: 1. Pickering TG, Hypertension and Lipid Trial Study Group. The use of 24-hour ambulatory monitoring in the assessment of antihypertensive therapy. Presented at the American Academy of Family Physicians 43rd Annual Assembly; September 24-29,1991; Washington, D.C. **2.** The Treatment of Mild Hypertension Research Group. The Treatment of Mild Hypertension Study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. *Arch Intern Med.* 1991;151:1413-1423. **3.** Lehtonen A, the Finnish Multicenter Study Group. Lowered levels of serum insulin, glucose, and cholesterol in hypertensive patients during treatment with doxazosin. *Curr Ther Res.* 1990;47:278-284.

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS

Syncope and "First-dose" Effect:

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

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

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

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

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

PRECAUTIONS

General

1. Orthostatic Hypotension:

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

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

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

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

2. Impaired liver function:

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

3. Leukopenia/Neutropenia:

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

Information for Patients:

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

Drug Interactions:

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

Drug/Laboratory test interactions:

None known.

Cardiac Toxicity in Animals:

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

Carcinogenesis, Mutagenesis and Impairment of Fertility:

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

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

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

Pregnancy

Teratogenic Effects, Pregnancy Category B. Studies in rabbits and rats at daily oral doses of up to 40 and 20 mg/kg, respectively (150 and 75 times the maximum recommended daily dose of 16 mg, assuming a patient weight of 60 kg), have revealed no evidence of harm to the fetus. The rabbit study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA should be used during pregnancy only if clearly needed.

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

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

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

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

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

TABLE 1
ADVERSE REACTIONS DURING PLACEBO CONTROLLED STUDIES

		DOXAZOSIN (N=339)	PLACEBO (N=336)
CARDIOVASCULAR:	Dizziness	19%	9%
	Vertigo	2%	1%
	Postural Hypotension	0.3%	0%
	Edema	4%	3%
	Palpitation	2%	3%
	Arrhythmia	1%	0%
	Hypotension	1%	0%
	Tachycardia	0.3%	1%
	Peripheral Ischemia	0.3%	0%
SKIN APPENDAGES:	Rash	1%	1%
	Pruritus	1%	1%
MUSCULOSKELETAL:	Arthralgia/Arthritis	1%	0%
	Muscle Weakness	1%	0%
	Myalgia	1%	0%
CENTRAL & PERIPHERAL N.S.:	Headache	14%	16%
	Paresthesia	1%	1%
	Kinetic Disorders	1%	0%
	Ataxia	1%	0%
	Hypertonia	1%	0%
	Muscle Cramps	1%	0%
AUTONOMIC:	Mouth Dry	2%	2%
	Flushing	1%	0%
SPECIAL SENSES:	Vision Abnormal	2%	1%
	Conjunctivitis/Eye Pain	1%	1%
	Tinnitus	1%	0.3%
PSYCHIATRIC:	Somnolence	5%	1%
	Nervousness	2%	2%
	Depression	1%	1%
	Insomnia	1%	1%
	Sexual Dysfunction	2%	1%
GASTROINTESTINAL:	Nausea	3%	4%
	Diarrhea	2%	3%
	Constipation	1%	1%
	Dyspepsia	1%	1%
	Flatulence	1%	1%
	Abdominal Pain	0%	2%
	Vomiting	0%	1%
RESPIRATORY:	Rhinitis	3%	1%
	Dyspnea	1%	1%
	Epistaxis	1%	0%
URINARY:	Polyuria	2%	0%
	Urinary Incontinence	1%	0%
	Micturation Frequency	0%	2%
GENERAL:	Fatigue/Malaise	12%	6%
	Chest Pain	2%	2%
	Asthenia	1%	1%
	Face Edema	1%	0%
	Pain	2%	2%

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

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

OVERDOSAGE

No data are available in regard to overdosage in humans.

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

DOSAGE AND ADMINISTRATION

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

HOW SUPPLIED

CARDURA (doxazosin mesylate) is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin.

CARDURA® TABLETS are available as 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) scored tablets.

Bottles of 100: 1 mg (NDC 0049-2750-66), 2 mg (NDC 0049-2760-66), 4 mg (NDC 0049-2770-66), 8 mg (NDC 0049-2780-66)

Recommended Storage: Store below 86°F(30°C).

CAUTION: Federal law prohibits dispensing without prescription.

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Pfizer Roerig

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VOLUME 15 NUMBER 10

Diabetes Care

American Diabetes Association®

Diabetes Care publishes original articles and reviews of human and clinical research intended to increase knowledge, stimulate research, and promote better management of people with diabetes mellitus. Emphasis is on human studies reporting on the pathophysiology and treatment of diabetes and its complications; genetics; epidemiology; psychosocial adaptation; education; and the development, validation, and application of accepted and new therapies. Topics covered are of interest to clinically oriented physicians, researchers, epidemiologists, psychologists, diabetes educators, and other professionals.

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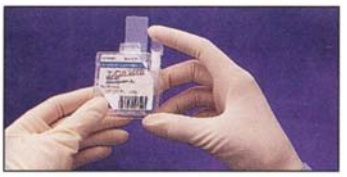

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- The DCA 2000 Analyzer makes it easy to follow the clinical guidelines for regular HbA_{1c} testing.*

*Clinical guidelines: Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 12:365-68, 1989.

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The DCA 2000™ Analyzer

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Authors should submit diskettes with the final version of their manuscripts, along with the typed revised manuscript. (Do not send diskettes with the initial submission.) All diskettes must be accompanied by 3 accurate double-spaced paper copies of the manuscript.

Either 3.5 or 5.25-inch diskettes can be used, and any major word processing program is acceptable. Diskettes may be produced on IBM, IBM-compatible, Apple, or Wang computers.

Diskettes must be labeled with the following information: 1) author's name, 2) article title, and 3) software and hardware used. Detailed instructions for diskette preparation and submission appear in the instructions for author's guidelines in the first issue of every volume.

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Diabetes is typically monitored using glucose and glycated hemoglobin (HbA_{1c}) tests. A glucose assay can be performed during a patient visit, yet the test only represents diabetic control at that time. Glycated hemoglobin results reflect six to eight weeks of clinical history, yet testing complexities can delay results.

When a normal glucose result is contrasted with an abnormal glycated hemoglobin result, the physician faces a diagnostic dilemma: Should therapy be adjusted, or should control be presumed and reinforced based on the glucose result? Normal fluctuations in glucose add risk to the latter course, often resulting in patient call-backs and repeat testing for diagnostic confirmation. ***With the availability of rapid results measuring a clinically significant timeframe, RoTAG provides a solution to this diagnostic dilemma.***

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RoTAG correlates well with fasting glucose and glycated hemoglobin, while it offers clear advantages: RoTAG provides a more immediate view of patient status than glycated hemoglobin, and it is not subject to the potential interferences associated with these tests. RoTAG may also be more reliable than glucose tests due to constant glucose fluctuations, which may be confused with changes in diabetic control.

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Guidelines for Interpretation

Glucose	RoTAG	HbA_{1c}	Interpretation
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^	^	—	Out of control within the past three weeks
^	^	^	Newly diagnosed or uncontrolled diabetic
—	—	^	Recently returned to control
—	^	^	Out of control over the past one to eight weeks

— Normal ^ Elevated

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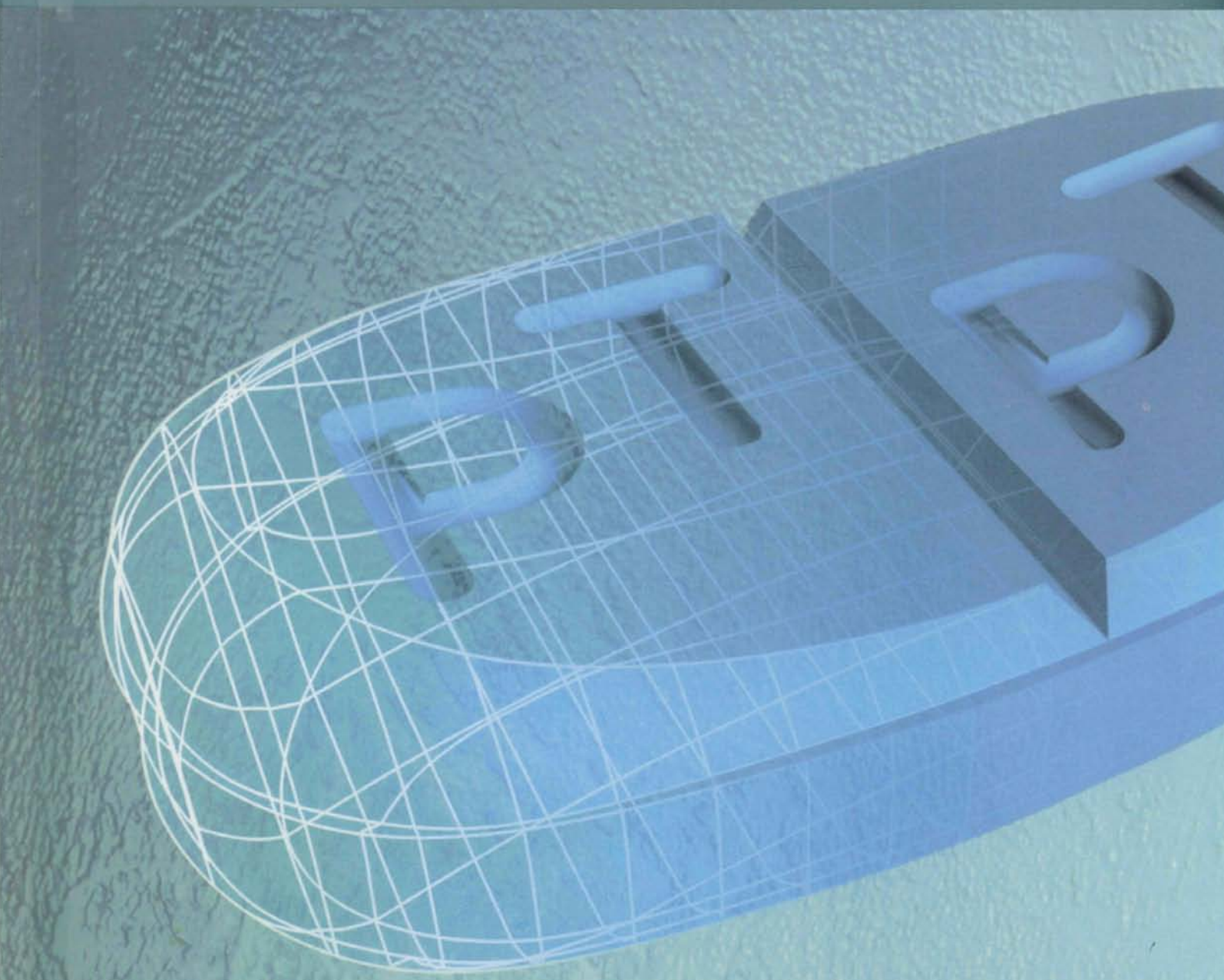

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GLYNASE PresTab: Designed for greater flexibility

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*Upjohn Utility Patent #4735805.

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GLYNASE PresTab was designed to help you meet your management goals. Now, as an adjunct to diet and exercise, your patients can get the trusted benefits of glyburide efficacy and safety†[1]—with ease of titration and improved absorption. Patients should be retitrated when transferred from Micronase® Tablets (glyburide) or other oral hypoglycemic agents.

†All sulfonylureas are associated with a risk of hypoglycemia. Proper patient selection, dosage, and instructions are important.

Please see the following page for brief summary of prescribing information.

GLYNASE™ PRESTAB™

Tablets (glyburide) **3mg**

Designed with management in mind

GLYNASE™ PRESTAB™

Tablets (glyburide) 3mg

Ease of titration towards maximum efficacy

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- The 1.5-mg tablet may be easily broken to provide the infrequent .75-mg dose.
- Patients should be retitrated when transferred from Micronase® (glyburide) or other oral hypoglycemic agents.

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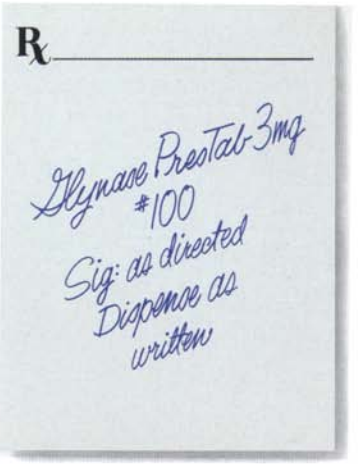
Usual Starting Dose	1.5 mg to 3 mg	2.5 mg to 5 mg	5 mg	250 mg
Daily Dosage Range	.75 mg to 12 mg	1.25 mg to 20 mg	2.5 mg to 40 mg	100 mg to 750 mg



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(glyburide)

INDICATIONS AND USAGE

GLYNASE PresTab Tablets are indicated as an adjunct to diet to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (type II) whose hyperglycemia cannot be satisfactorily controlled by diet alone. During maintenance programs, GLYNASE PresTab should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Controlling blood glucose in non-insulin-dependent diabetes has not been definitely established to be effective in preventing the long-term cardiovascular or neural complications of diabetes.

CONTRAINDICATIONS

1.Known hypersensitivity or allergy to the drug.
2.Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
3.Type I diabetes mellitus, as sole therapy.

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.1970;19(suppl 2):747-830).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 g per day) had a rate of cardiovascular mortality approximately 2½ 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 GLYNASE PresTab 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

Bioavailability studies have demonstrated that GLYNASE PresTab Tablets 3mg provide serum glyburide concentrations that are not bioequivalent to those from MICRONASE Tablets 5 mg. Therefore, the dose should be retitrated when a patient is transferred from MICRONASE or Diaßeta or other oral *hypoglycemic agents*.

General

Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection and dosage and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may 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 may be difficult to recognize in the elderly and in people who are taking ß-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. **Loss of Control of Blood Glucose:** In stabilized diabetic patients 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 GLYNASE PresTab and administer insulin. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as secondary failure. **Information for Patients**: Patients should be informed of the potential risks and advantages of GLYNASE PresTab and of alternative modes of therapy. They also should be informed about the importance of adherence 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 should also be explained.

Laboratory Tests

Response to GLYNASE PresTab Tablets should be monitored by frequent urine glucose tests and periodic blood glucose tests. Measurement of glycosylated hemoglobin levels may be helpful in some patients.

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 ß-adrenergic blocking agents.

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. It is not known whether this reaction also occurs with intravenous, topical, or vaginal miconazole.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in rats at doses up to 300 mg/kg/day for 18 months showed no carcinogenic effects. Glyburide is nonmutagenic when studied in the Salmonella microsome test (Ames test) and in the DNA damage/alkaline elution assay. No drug-related effects were noted in a 2-year oncogenicity study of glyburide in mice.

Pregnancy

Teratogenic Effects: Pregnancy Category B

Reproduction studies in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus due to glyburide. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Many experts recommend that insulin be used during pregnancy to maintain blood glucose 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 for agents with prolonged half-lives. If used during pregnancy, GLYNASE PresTab should be discontinued at least 2 weeks before the expected delivery date.

Nursing Mothers

Some sulfonylurea drugs are known to be excreted in human milk. Therefore, a decision should be made whether to discontinue nursing or discontinue drug. Insulin therapy should be considered if diet alone is not adequate for controlling blood glucose.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Hypoglycemia: See Precautions and Overdosage sections. **Gastrointestinal Reactions:** Cholestatic jaundice and hepatitis may occur rarely; GLYNASE PresTab Tablets should be discontinued if this occurs. Liver function abnormalities have been reported. Gastrointestinal disturbances (eg, nausea, epigastric fullness, and heartburn) are the most common reactions and occurred in 1.8% of patients during clinical trials. They tend to be dose related and may disappear when the dose is reduced. **Dermatologic Reactions:** Allergic skin reactions (eg, pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions) occurred in 1.5% of patients during trials. These may be transient and may disappear despite continued use of glyburide; 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 and disulfiramlike reactions have been reported with sulfonylureas; however, hepatic porphyria has not been reported with glyburide, and disulfiramlike reactions have been reported very rarely. Cases of hyponatremia have been reported with glyburide 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 (ADH). The syndrome of inappropriate ADH (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 or increase release of ADH, or both. **Other Reactions:** Changes in accommodation or blurred vision, or both, have been reported with glyburide and other sulfonylureas. In addition to dermatologic reactions, allergic reactions such as angioedema, arthralgia, myalgia, and vasculitis have been reported.

OVERDOSAGE

Overdosage of sulfonylureas, including glyburide, can produce hypoglycemia. Mild hypoglycemic symptoms should be treated aggressively with oral glucose and adjustments in drug dosage or meal patterns, or both. Close monitoring should continue until the physician is assured that patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurologic 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 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, because hypoglycemia may recur after apparent clinical recovery.

HOW SUPPLIED

GLYNASE PresTab Tablets are available as 1.5-mg and 3-mg tablets.

Caution: Federal law prohibits dispensing without a prescription.

Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in well closed containers with safety closures. Keep container tightly closed.

Diaßeta is a trademark of Hoechst-Roussel Pharmaceuticals, Inc.

The Upjohn Company
Kalamazoo, MI 49001 USA B-1-S

Reference

1. Data on file, The Upjohn Company, Kalamazoo, Mich.

Upjohn The Upjohn Company
Kalamazoo, MI 49001 June 1992 USJ4067.00

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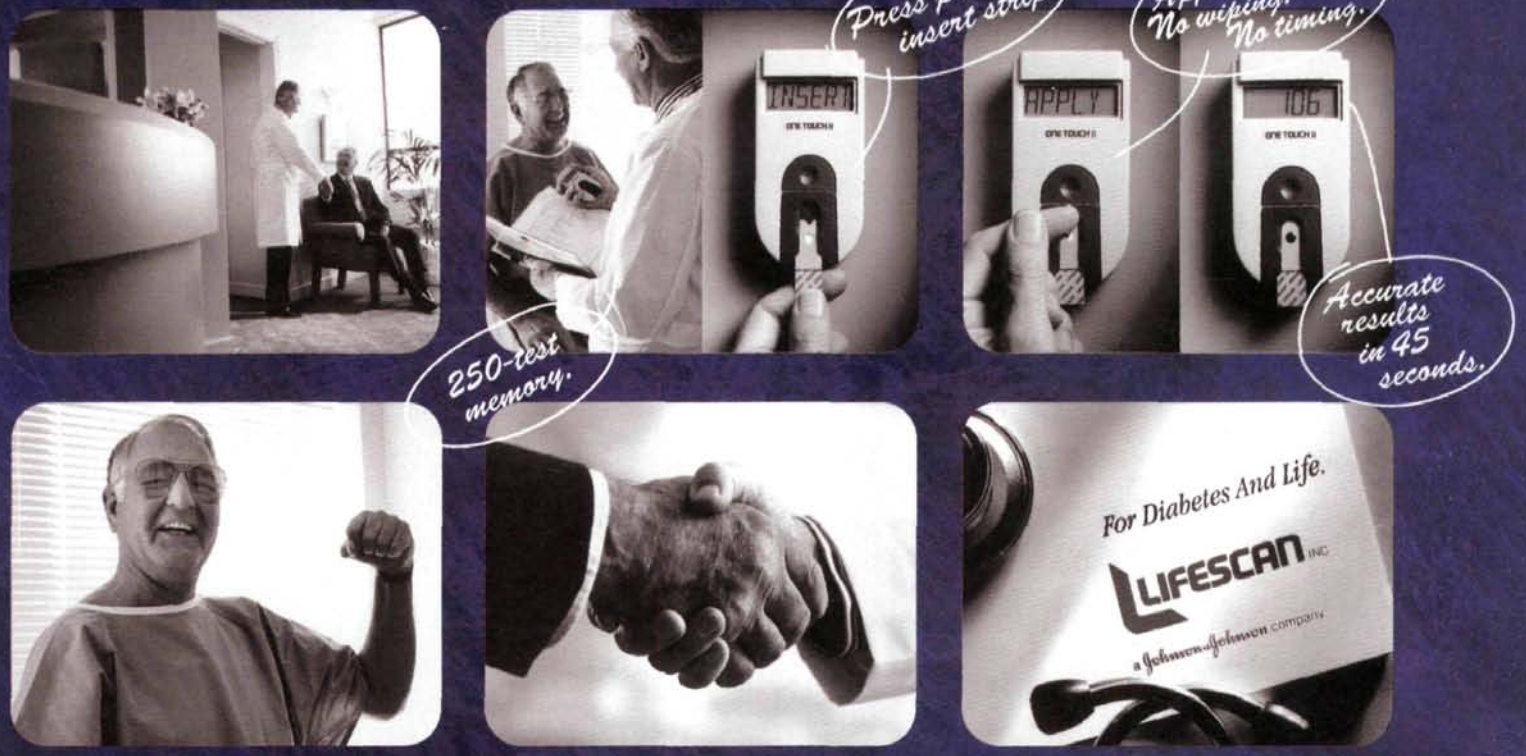

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The ONE TOUCH® II Blood Glucose Monitoring System's proven no-wipe technology is so easy to use and accurate in everyday life, it can actually lead to a better quality of life for your patients. Perhaps that's why it's the meter recommended by more specialists and diabetes educators.* Available at drug stores and home healthcare centers, it comes with a 30-day, money-back guarantee. Plus it's backed with a 24-hour, toll-free consumer technical services line for your patients. And a 24-hour Healthcare Professional Hotline for *your* patience. Call 1 800 524-7226. LifeScan, for diabetes and life.

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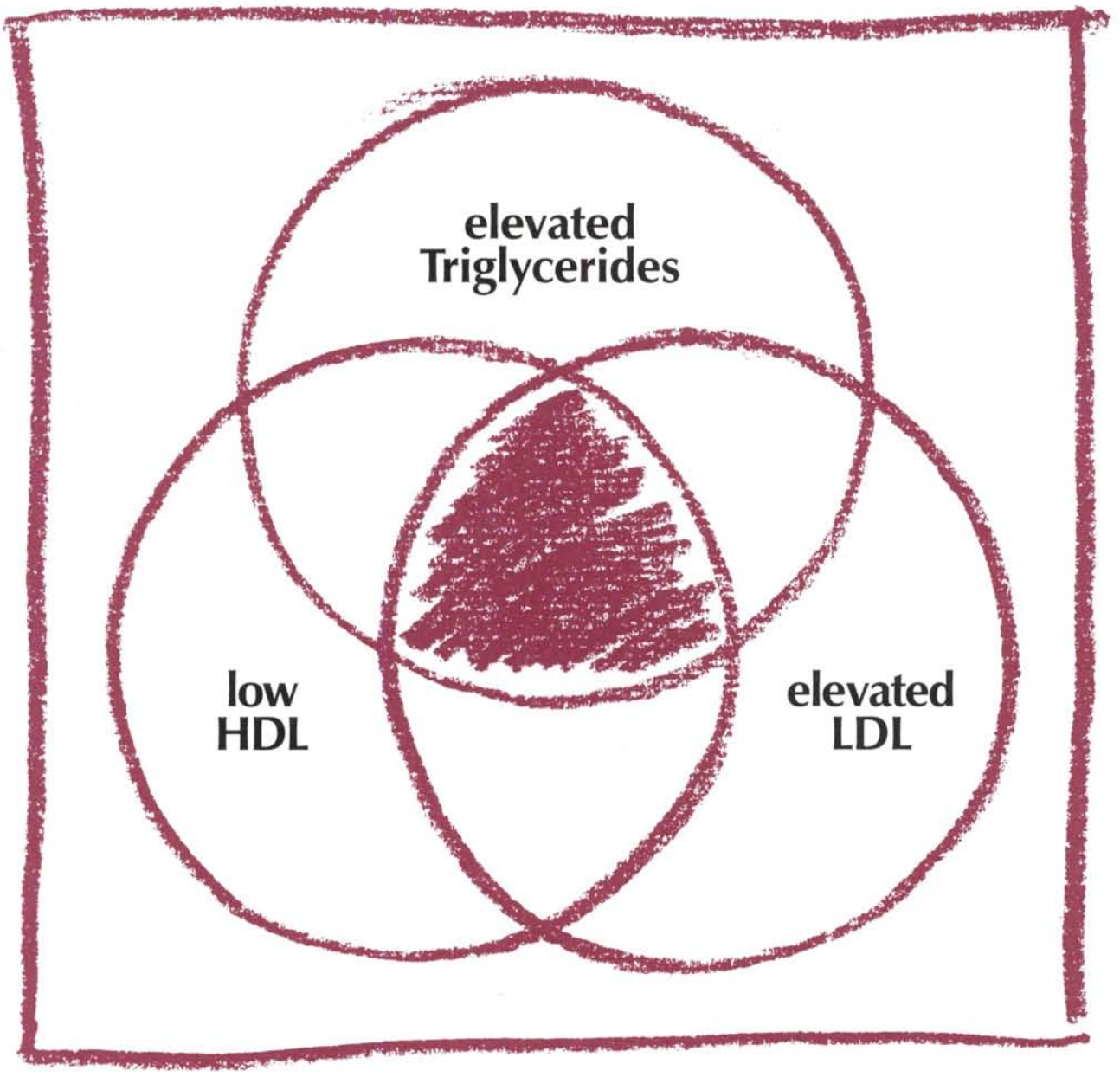
Reduce the risk of developing CHD in patients with the triad of risk...



As an adjunct to diet, after an inadequate response to exercise, dietary therapy, weight loss and trial of other pharmacologic agents (such as bile acid sequestrants and nicotinic acid)

LOPID®

(gemfibrozil) 600-mg Tablets BID

REDUCES THE RISK OF DEVELOPING CHD
IN PATIENTS WITH THE TRIAD OF RISK

LOPID is indicated as adjunctive therapy to diet for reducing the risk of developing coronary heart disease **only** in Type IIb patients:

- Without history of or symptoms of existing coronary heart disease
- Who have had an inadequate response to weight loss, dietary therapy, exercise, and other pharmacologic agents (such as bile acid sequestrants and nicotinic acid, known to reduce LDL- and raise HDL-cholesterol)

and

- Who have the following triad of lipid abnormalities: low HDL-cholesterol levels in addition to elevated LDL-cholesterol and elevated triglycerides

In addition:

- The potential benefit of gemfibrozil in treating Type IIa patients with elevations of LDL-cholesterol only is not likely to outweigh the risks
- LOPID is not indicated for the treatment of patients with low HDL-cholesterol as their only lipid abnormality

LOPID is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil

LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis

Caution should be exercised when anticoagulants are given in conjunction with LOPID

Please see last page of this advertisement for brief summary of prescribing information.

PARKE-DAVIS BOOTS PHARMACEUTICALS

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

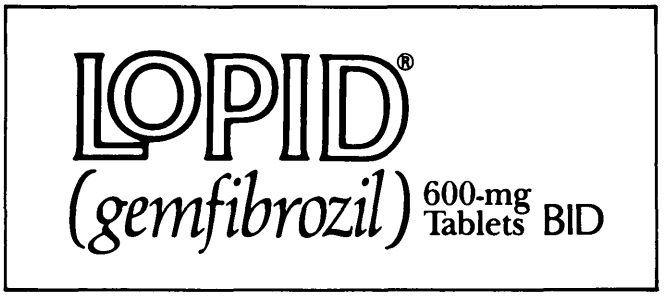
Before prescribing, please see full prescribing information. A Brief Summary follows.

CONTRAINDICATIONS

1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.
2. Preexisting gallbladder disease (see WARNINGS).
3. Hypersensitivity to gemfibrozil.

WARNINGS

1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 44%, higher age-adjusted total mortality in the clofibrate-treated than in a comparable placebo-treated control group during the trial period. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.



Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the Lopid and placebo group is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to Lopid primarily due to cancer deaths observed during the open-label extension.

During the 5 year primary prevention component of the Helsinki Heart Study mortality from any cause was 44 (2.2%) in the Lopid group and 43 (2.1%) in the placebo group; including the 3.5 year follow-up period since the trial was completed, cumulative mortality from any cause was 101 (4.9%) in the Lopid group and 83 (4.1%) in the group originally randomized to placebo (hazard ratio 1.20 in favor of placebo). Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the Lopid and placebo groups at year-5 or at year-8.5 is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to Lopid at the 8.5 year follow-up (65 Lopid versus 45 placebo noncoronary deaths).

The incidence of cancer (excluding basal cell carcinoma) discovered during the trial and in the 3.5 years after the trial was completed was 51 (2.5%) in both originally randomized groups. In addition, there were 16 basal cell carcinomas in the group originally randomized to Lopid and 9 in the group originally randomized to placebo ($p = 0.22$). There were 30 (1.5%) deaths attributed to cancer in the group originally randomized to Lopid and 18 (0.9%) in the group originally randomized to placebo ($p = 0.11$). Adverse outcomes, including coronary events, were higher in gemfibrozil patients in a corresponding study in men with a history of known or suspected coronary heart disease in the secondary prevention component of the Helsinki Heart Study. See CLINICAL PHARMACOLOGY section in full prescribing information which includes the following: The secondary prevention component of the Helsinki Heart Study was conducted over 5 years in parallel and at the same centers in Finland in 628 middle-aged males excluded from the primary prevention component of the Helsinki Heart Study because of a history of angina, myocardial infarction or unexplained ECG changes. The primary efficacy endpoint of the study was cardiac events (the sum of fatal and non-fatal myocardial infarctions and sudden cardiac deaths). The hazard ratio (Lopid:placebo) for cardiac events was 1.47 (95% confidence limits 0.88-2.48, p=0.14). Of the 35 patients in the Lopid group who experienced cardiac events, 12 patients suffered events after discontinuation from the study. Of the 24 patients in the placebo group with cardiac events, 4 patients suffered events after discontinuation from the study. There were 17 cardiac deaths in the Lopid group and 8 in the placebo group (hazard ratio 2.18; 95% confidence limits 0.94-5.05, p=0.06). Ten of these deaths in the Lopid group and 3 in the placebo group occurred after discontinuation from therapy. In this study of patients with known or suspected coronary heart disease, no benefit from Lopid treatment was observed in reducing cardiac events or cardiac deaths. Thus, Lopid has shown benefit only in selected dyslipidemic patients *without* suspected or established coronary heart disease. Even in patients with coronary heart disease and the triad of elevated LDL-cholesterol, elevated triglycerides, plus low HDL-cholesterol, the possible effect of Lopid on coronary events has not been adequately studied.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.
3. Since a reduction of mortality from coronary heart disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.
4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.
5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. IN VIRTUALLY ALL PATIENTS WHO HAVE HAD AN UNSATISFACTORY LIPID RESPONSE TO EITHER DRUG ALONE, ANY POTENTIAL LIPID BENEFIT OF COMBINED THERAPY WITH LOVASTATIN AND GEMFIBROZIL DOES NOT OUTWEIGH THE RISKS OF SEVERE MYOPATHY, RHABDOMYOLYSIS, AND ACUTE RENAL FAILURE (see Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.
6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS

1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.
2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.
3. **Drug Interactions** – (A) **HMG-CoA reductase inhibitors:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin (or other HMG-CoA reductase inhibitors) and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats at 0.2 and 2 times the human dose (based on surface area, mg/meter^2). The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant ($p = 0.1$). Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors. The higher dose female rats had a significant increase in the combined incidence of benign, and malignant liver neoplasms.

Long-term studies have been conducted in mice at 0.1 and 1 times the human dose (based on surface area). There were no statistically significant differences from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately 0.6 and 2 times the human dose (based on surface area) to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category C** – Lopid has been shown to produce adverse effects in rats and rabbits at doses between 0.5 and 3 times the human dose (based on surface area) but no developmental toxicity or teratogenicity among offspring of either species. There are no adequate and well-controlled studies in pregnant women. Lopid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of Lopid to female rats at 0.6 and 2 times the human dose (based on surface area) before and throughout gestation caused a dose-related decrease in conception rate and, at the high dose, an increase in stillborns and a slight reduction in pup weight during lactation. There were also dose-related increased skeletal variations. Anophthalmia occurred, but rarely.

Administration of 0.6 and 2 times the human dose (based on surface area) of Lopid to female rats from gestation day 15 through weaning caused dose-related decreases in birth weight and suppressions of pup growth during lactation.

Administration of 1 and 3 times the human dose (based on surface area) of Lopid to female rabbits during organogenesis caused a dose-related decrease in litter size and at the high dose, an increased incidence of parietal bone variations.

6. **Nursing Mothers** – It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for Lopid in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.
8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.
9. **Kidney Function** – There have been reports of worsening renal insufficiency upon the addition of Lopid therapy in individuals with baseline plasma creatinine > 2.0 mg/dL. In such patients, the use of alternative therapy should be considered against the risks and benefits of a lower dose of Lopid.
10. **Use in Children** – Safety and efficacy in children and adolescents have not been established.

ADVERSE REACTIONS

In the double-blind controlled phase of the primary prevention component of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group:

	LOPID (N=2046)	PLACEBO (N=2035)
	Frequency in percent of subjects	
Gastrointestinal reactions	34.2	23.8
Dyspepsia	19.6	11.9
Abdominal pain	9.8	5.6
Acute appendicitis (histologically confirmed in most cases where data were available)	1.2	0.6
Atrial fibrillation	0.7	0.1
Adverse events reported by more than 1% of subjects, but without a significant difference between groups:		
Diarrhea	7.2	6.5
Fatigue	3.8	3.5
Nausea/Vomiting	2.5	2.1
Eczema	1.9	1.2
Rash	1.7	1.3
Vertigo	1.5	1.3
Constipation	1.4	1.3
Headache	1.2	1.1

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects in the primary prevention component, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study. Gallbladder surgery was also performed more frequently in the Lopid group compared to placebo (1.9% vs. 0.3%, $p = 0.07$) in the secondary prevention component. A statistically significant increase in appendectomy in the gemfibrozil group was seen also in the secondary prevention component (6 on gemfibrozil vs. 0 on placebo, $p = 0.014$).

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of MUSCULOSKELETAL SYMPTOMS (see WARNINGS), and to ABNORMAL LIVER FUNCTION TESTS and HEMATOLOGIC CHANGES (see PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil treated patients in other controlled clinical trials of 805 patients. Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility, renal dysfunction; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION

The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

OVERDOSAGE

While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

HOW SUPPLIED

Lopid (Tablet 737), white, elliptical, film-coated, scored tablets, each containing 600 mg gemfibrozil, are available as follows:

N 0071-0737-20 Bottles of 60
N 0071-0737-30 Bottles of 500
N 0071-0737-40 Unit dose packages of 100 (10 strips of 10 tablets each)
Parcode® No. 737

Storage: Store below 30° C (86° F).

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Caution – Federal law prohibits dispensing without prescription. 0737G015

Revised April 1992

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PD-56-JA-8080-B1(072)

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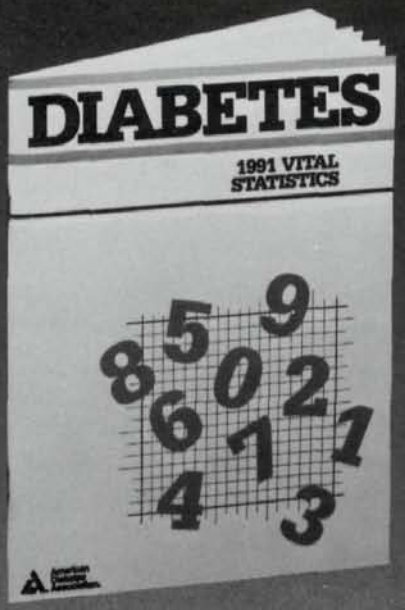

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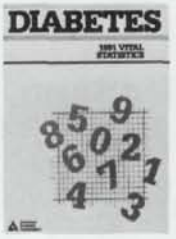

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THEY WERE CAREFREE...

They were raised in a simpler time, before sugar-free and fat-free. Now hypertension, often with elevated cholesterol and blood sugar, enters the picture...

NOW THEY'RE CONCERNED...

Today's hypertensives with new concerns...

THE CARDURA

*Adapted from the interim (12 months) results of the Treatment of Mild Hypertension Study, a randomized, double-blind, placebo-controlled trial of a nutritional-hygienic regimen along with various drug therapies. All drugs (except acebutolol) were given initially in low doses. If the patient showed a diastolic blood pressure more than 95 mm Hg on three successive follow-up visits, the dosage was doubled. If blood pressure remained elevated, a second drug (chlorthalidone, except for chlorthalidone group, which was given enalapril) was added. Mean diastolic blood pressure was lowered in the various drug groups with median dosages, as follows: doxazosin (2 mg/day), 12.0 mm Hg; enalapril (5 mg/day), 12.2 mm Hg; chlorthalidone (15 mg/day), 13.1 mm Hg; and acebutolol (400 mg/day), 13.7 mm Hg (n=847; $P<0.01$ vs placebo).

†n=128; $P<0.01$ vs placebo. In a pooled analysis of placebo-controlled studies with about 300 predominantly normocholesterolemic patients per treatment group, CARDURA produced a small decrease in total cholesterol (-2.7%) and LDL cholesterol (-4.3%) and a small increase in the HDL/total cholesterol ratio (+4.3%).

‡Adapted from Lehtonen et al[2] (n=77; after 26 weeks: $P<0.001$ compared with week 0 for blood pressure and insulin, $P<0.05$ compared with week 0 for glucose).

GENERATION

Choose CARDURA: first-line therapy for a new generation of hypertensives.

Choose CARDURA for blood pressure control that doesn't jeopardize blood lipids.

In the Treatment of Mild Hypertension Study, CARDURA lowered diastolic blood pressure (mean 12.0 mm Hg) as effectively as enalapril, chlorthalidone, and acebutolol[1*]

CARDURA lowered blood pressure with a small increase in the HDL/total cholesterol ratio (+2.4%)* in the same study.[1†] The clinical significance of these changes is uncertain. Cholesterol is just one parameter to consider when selecting the best individualized therapy for a given patient

Choose CARDURA for blood pressure control that doesn't compromise blood sugar.

CARDURA controlled diastolic blood pressure without an adverse effect on glucose tolerance or insulin control[2‡]

CARDURA is well tolerated. In placebo-controlled studies, only three common side effects were reported significantly more often than placebo: dizziness, somnolence, and fatigue.[§]

Only 2% of patients discontinued therapy due to adverse effects—the same as with placebo

§ These were generally mild and transient. Syncope has been reported, but rarely (<1%).

ONCE-A-DAY

CARDURA®

(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

HYPERTENSION CONTROL FOR A NEW GENERATION.

Please see brief summary on last page.

ONCE-A-DAY

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(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS

Syncope and "First-dose" Effect:

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

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

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

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

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

PRECAUTIONS

General

1. Orthostatic Hypotension:

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

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

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

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

2. Impaired liver function:

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

3. Leukopenia/Neutropenia:

Analysis of hematologic data from patients receiving CARDURA in controlled clinical trials showed that the mean WBC (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. A search through a data base of 2400 patients revealed 4 in which drug-related neutropenia could not be ruled out. Two had a single low value on the last day of treatment. Two had stable, non-progressive neutrophil counts in the 1000/mm^3 range over periods of 20 and 40 weeks. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA. No patients became symptomatic as a result of the low WBC or neutrophil counts.

Information for Patients:

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

Drug Interactions:

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

Drug/Laboratory test interactions:

None known.

Cardiac Toxicity in Animals:

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

Carcinogenesis, Mutagenesis and Impairment of Fertility:

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

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

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

Pregnancy

Teratogenic Effects, Pregnancy Category B. Studies in rabbits and rats at daily oral doses of up to 40 and 20 mg/kg, respectively (150 and 75 times the maximum recommended daily dose of 16 mg, assuming a patient weight of 60 kg), have revealed no evidence of harm to the fetus. The rabbit study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA should be used during pregnancy only if clearly needed.

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

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

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

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

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

TABLE 1
ADVERSE REACTIONS DURING PLACEBO CONTROLLED STUDIES

		DOXAZOSIN (N=339)	PLACEBO (N=336)
CARDIOVASCULAR:	Dizziness	19%	9%
	Vertigo	2%	1%
	Postural Hypotension	0.3%	0%
	Edema	4%	3%
	Palpitation	2%	3%
	Arrhythmia	1%	0%
	Hypotension	1%	0%
	Tachycardia	0.3%	1%
	Peripheral Ischemia	0.3%	0%
SKIN APPENDAGES:	Rash	1%	1%
	Pruritus	1%	1%
MUSCULOSKELETAL:	Arthralgia/Arthritis	1%	0%
	Muscle Weakness	1%	0%
	Myalgia	1%	0%
CENTRAL & PERIPHERAL N.S.:	Headache	14%	16%
	Paresthesia	1%	1%
	Kinetic Disorders	1%	0%
	Ataxia	1%	0%
	Hypertonia	1%	0%
	Muscle Cramps	1%	0%
AUTONOMIC:	Mouth Dry	2%	2%
	Flushing	1%	0%
SPECIAL SENSES:	Vision Abnormal	2%	1%
	Conjunctivitis/Eye Pain	1%	1%
	Tinnitus	1%	0.3%
PSYCHIATRIC:	Somnolence	5%	1%
	Nervousness	2%	2%
	Depression	1%	1%
	Insomnia	1%	1%
	Sexual Dysfunction	2%	1%
GASTROINTESTINAL:	Nausea	3%	4%
	Diarrhea	2%	3%
	Constipation	1%	1%
	Dyspepsia	1%	1%
	Flatulence	1%	1%
	Abdominal Pain	0%	2%
	Vomiting	0%	1%
RESPIRATORY:	Rhinitis	3%	1%
	Dyspnea	1%	1%
	Epistaxis	1%	0%
URINARY:	Polyuria	2%	0%
	Urinary Incontinence	1%	0%
	Micturation Frequency	0%	2%
GENERAL:	Fatigue/Malaise	12%	6%
	Chest Pain	2%	2%
	Asthenia	1%	1%
	Face Edema	1%	0%
	Pain	2%	2%

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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

HOW SUPPLIED

CARDURA (doxazosin mesylate) is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin.

CARDURA® TABLETS are available as 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) scored tablets.

Bottles of 100: 1 mg (NDC 0049-2750-66), 2 mg (NDC 0049-2760-66), 4 mg (NDC 0049-2770-66), 8 mg (NDC 0049-2780-66)

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65-4538-00-0 Issued Nov 1990

References: 1. The Treatment of Mild Hypertension Research Group. The Treatment of Mild Hypertension Study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. *Arch Intern Med.* 1991;151:1413-1423. **2.** Lehtonen A, the Finnish Multicenter Study Group. Lowered levels of serum insulin, glucose, and cholesterol in hypertensive patients during treatment with doxazosin. *Curr Ther Res.* 1990;47:278-284.

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 Printed in USA January 1992

American Diabetes Association.

Call 1-800-232-3472 Ext. 330 For Registration Details

40TH

Annual Advanced Postgraduate Course

FAIRMONT HOTEL

JANUARY 22 - 24, 1993

SAN FRANCISCO, CALIFORNIA

CHALLENGES AND CONTROVERSIES IN THE MANAGEMENT OF DIABETES AND OTHER ENDOCRINE DISORDERS

San Francisco is full of surprises. It's a place where dragons, bocce ball players, sidewalk stringed quartets, kite fliers and calligraphy street signs are a part of the everyday landscape...where you can scale home-grown alps in antique cable cars, walk across the Pacific (on the Golden Gate Bridge), serpentine down a street that looks like a slalom run and island-hop by ferry. It's a city of all seasons with mild winters, springlike summers, views that rival Rio's and stores on a par with Paris.

San Francisco has been called a "window of the world." The way the hills rise steeply out of a sparkling, island-studded bay is reminiscent of Hong Kong. At other times, when the harbor's a wind-whipped green, San Francisco assumes a Nordic look. The Marina, a forest of sailboat spars, and Fisherman's Wharf, where the fishing fleet ties up, could be scenes painted in Portofino or St. Tropez. This is the far eastern edge of the Orient. The western edge of the continent. A port of gold.

Speakers

Sharon Anderson, MD
Associate Professor of Medicine
Oregon Health Sciences University
Portland, Oregon

John P. Bilezikian, MD
Professor of Medicine and of Pharmacology; Chief, Division of Endocrinology, Columbia University, College of Physicians and Surgeons
New York, New York

Andrew J.M. Boulton, MD
Reader in Medicine/Consultant Physician
Manchester Royal Infirmary
United Kingdom

Patrick J. Boyle, MD
Assistant Professor of Medicine
University of New Mexico
School of Medicine
Albuquerque, New Mexico

Glenn D. Braunstein, MD
Professor of Medicine, UCLA School of Medicine; Chairman, Department of Medicine, Cedars-Sinai Medical Center
Los Angeles, California

Brenda A. Broussard, RD, MPH
Nutrition Specialist
Indian Health Service Diabetes Program
Albuquerque, New Mexico

Michael Brownlee, MD
Professor of Medicine and Co-Director of Diabetes Research Center,
Albert Einstein College of Medicine
Bronx, New York

John D. Brunzell, MD
Professor of Medicine
University of Washington
School of Medicine
Seattle, Washington

Philip E. Cryer, MD
Professor of Medicine and Director of the Division of Endocrinology, Diabetes, and Metabolism,
Washington University
School of Medicine
St. Louis, Missouri

Mayer B. Davidson, MD
Professor of Medicine, UCLA School of Medicine; Director, Diabetes Program, Cedars-Sinai Medical Center
Los Angeles, California

Larry Deeb, MD
Endocrinologist
Children's Clinic
Tallahassee, Florida

Stefan S. Fajans, MD
Professor Emeritus (Active) of Internal Medicine
University of Michigan
School of Medicine
Ann Arbor, Michigan

Ruth Farkas-Hirsch, MS, RN, CDE
Diabetes Clinical Specialist,
University of Washington
School of Medicine
Seattle, Washington

John Foreyt, PhD
Director, Nutrition Research Center,
Baylor College of Medicine
Houston, Texas

John Galloway, MD
Clinical Research Fellow, Lilly Research Laboratories; Professor of Medicine,
Indiana University School of Medicine
Indianapolis, Indiana

James R. Gavin, III, MD, PhD
Senior Scientific Officer
Howard Hughes Medical Institute
Bethesda, Maryland

David Goldstein, MD
Professor of Pediatrics, Medicine, and Pathology
University of Missouri
School of Medicine
Columbia, Missouri

Douglas Greene, MD
Professor of Internal Medicine, Division Chief, Endocrinology & Metabolism; Director, Michigan Diabetes Research and Training Center
Ann Arbor, Michigan

Scott Grundy, MD, PhD
Professor of Internal Medicine & Biochemistry
University of Texas Southwestern Medical Center at Dallas
Dallas, Texas

Debra Haire-Joshu, PhD, RN
Director, Diabetes Education Center, DRTC, Research Associate Professor of Medicine, Washington University School of Medicine
St. Louis, Missouri

Deborah Hinnen, RN, MN, CDE
Program Director
Diabetes Treatment and Research Center
Wichita, Kansas

Irl Hirsch, MD
Director, Diabetes Care Center;
Associate Professor,
University of Washington
Seattle, Washington

Robert W. Jeffery, PhD
Professor of Epidemiology
University of Minnesota
School of Medicine
Minneapolis, Minnesota

Howard L. Judd, MD
Professor of Obstetrics and Gynecology,
UCLA; Executive Director, Division
of Reproductive Endocrinology,
UCLA and Cedars-Sinai
Los Angeles, California

John L. Kitzmiller, MD
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School of Medicine
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Clinical Nurse Specialist
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Professor of Medicine
SUNY Health Science Center at Brooklyn
Brooklyn, New York

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Professor of Physiology and
Biophysics; Co-Director State
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Consulting Associates
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Veterans Affairs Medical Center
Kansas City, Kansas

Duncan S. Wigg, PhD
Clinical Psychologist,
University of California-Irvine;
Department of Family Medicine-
Pepperdine University
Irvine, California

William Winter, MD
Associate Professor of Pathology and
Laboratory Medicine, Pediatrics, and
Immunology and Medical Microbiology
University of Florida
Gainesville, Florida

40th Advanced Postgraduate Course

The 40th Annual Advanced Postgraduate Course is presented in two concurrent tracks. Track I will feature sessions on diabetic neuropathy, new applications of standard therapy, unusual subsets of diabetes, controversies in clinical endocrinology, and upcoming therapies. Track II will provide an update on intensive insulin therapy, obesity as a risk factor, educational and counselling strategies for various ethnic populations, and the effects of standards of practice on the delivery of diabetes health care.

These advanced sessions have been specifically designed for endocrinologists, diabetologists, nurses, and other health care professionals who will benefit from an advanced program.

Program Objectives

1. To review the latest approaches in the management of type I and type II diabetes, and provide an overview of recent therapeutic developments.

2. To provide an update on current clinically-based research in the areas of malnutrition-related diabetes, Maturity-Onset Diabetes of Youth (MODY), and diabetes in the Black American.

3. To discuss issues of controversy on the topics of replacement estrogen therapy, the androgenized woman, and asymptomatic primary hyperparathyroidism.

4. To review the importance of obesity as a risk factor in patients with diabetes.

5. To compare and contrast effective treatment, educational, and counselling strategies for various ethnic populations.

P R O G R A M

Track I

FRIDAY, JANUARY 22, 1993

SESSION 1: ***Diabetic Neuropathy***

8:30 a.m. - 9:15 a.m. Pathophysiology and Results in New Clinical Studies with Aldose Reductase Inhibitors
Douglas Greene, MD

9:15 a.m. - 10:00 a.m. Unusual Clinical Aspects of Diabetic Neuropathy
Andrew J. M. Boulton, MD

10:00 a.m. - 11:00 a.m. Break

11:00 a.m. - 11:45 a.m. New Treatment Modalities for Diabetic Neuropathy
Aaron I. Vinik, MD

11:45 a.m. - 12:30 p.m. Hypoglycemia-Associated Autonomic Failure in the Absence of Autonomic Neuropathy
Philip E. Cryer, MD

SESSION 2: ***New Applications of Standard Therapy***

2:00 p.m. - 2:45 p.m. Microalbuminuria: Harbinger of Clinical Nephropathy?
Thomas Wiegmann, MD

2:45 p.m. - 3:30 p.m. Role of Antihypertensive Treatment in Early Diabetic Nephropathy
Leopoldo Raij, MD

3:30 p.m. - 4:15 p.m. Break

4:15 p.m. - 5:00 p.m. Do Low Protein Diets Delay Renal Insufficiency in Patients with Early Diabetic Nephropathy?
Sharon Anderson, MD

5:00 p.m. - 5:45 p.m. Alternative Drug Treatment of Hypertriglyceridemia in Diabetes
Scott Grundy, MD, PhD

SATURDAY, JANUARY 23, 1993

SESSION 3: ***Unusual Subsets of Diabetes Mellitus***

8:30 a.m. - 9:15 a.m. Type II Diabetes in Black Americans
Harold E. Lebovitz, MD

9:15 a.m. - 10:00 a.m. Atypical Diabetes in Younger Black Americans
William Winter, MD

10:00 a.m. - 11:00 a.m. Break

Track I

11:00 a.m. - 11:45 a.m. Diabetes When Food is Scarce (Malnutrition-Related Diabetes)
Donald E. McMillan, MD

11:45 a.m. - 12:30 p.m. Inheritance and Pathogenesis of "Maturity-Onset Diabetes of Youth" (MODY)
Stefan S. Fajans, MD

SESSION 4: ***Controversies in Clinical Endocrinology***

2:00 p.m. - 2:45 p.m. Replacement Estrogen Therapy - Yes Or No? If So, How?
Howard L. Judd, MD

2:45 p.m. - 3:30 p.m. The Androgenized Woman - From Simple Hirsutism to Virilization
Glenn D. Braunstein, MD

3:30 p.m. - 3:45 p.m. Break

3:45 p.m. - 4:30 p.m. New Approaches to the Evaluation and Treatment of Patients with Asymptomatic Primary Hyperparathyroidism
John P. Bilezikian, MD

SUNDAY, JANUARY 24, 1993

SESSION 5: ***Therapies Just Around the Corner***

8:00 a.m. - 8:40 a.m. Future Therapies of IDDM: Are We There Yet?
Robert Ratner, MD

8:40 a.m. - 9:20 a.m. Maintenance of Endogenous Insulin Secretion in New Onset Type I Diabetes
William Riley, MD

9:20 a.m. - 10:00 a.m. New Insulins and Insulinotropic Agents
John Galloway, MD

10:00 a.m. - 11:00 a.m. Break

11:00 a.m. - 11:30 a.m. Aminoguanidine - An Inhibitor of Advanced Glycosylation End Products (AGE)
Michael Brownlee, MD

11:30 a.m. - 12:00 noon Metformin, Phenformin's (DBI) Cousin
Mayer B. Davidson, MD

12:00 noon - 12:30 p.m. Thiazolidinediones - Restorer of Insulin Sensitivity
Jerrold M. Olefsky, MD

S C H E D U L E

Track II

FRIDAY, JANUARY 22, 1993

SESSION 1: ***Intensive Insulin Therapy Update***

CHAIR: *Ruth Farkas-Hirsch, MS, RN, CDE*

8:00 a.m. - 8:40 a.m. Complications of Intensive Therapy
Patrick J. Boyle, MD

8:40 a.m. - 9:20 a.m. Controversies of Insulin Management During Surgery
Irl Hirsch, MD

9:20 a.m. - 10:00 a.m. Critical Role of the Nurse Specialist in Intensive Management
Davida Kruger, MSN, RN, CDE

10:00 a.m. - 11:00 a.m. Break

11:00 a.m. - 11:45 a.m. Assessment of Glycemic Control
David Goldstein, MD

11:45 a.m. - 12:30 p.m. Trends in the Management of Brittle Diabetes
David S. Schade, MD

SESSION 2: ***Obesity As a Risk Factor: More Than Meets the Eye***

CHAIR: *Debra Haire-Joshu, PhD, RN*

2:00 p.m. - 2:45 p.m. Dilemma of Weight Gain After Smoking Cessation
Debra Haire-Joshu, PhD, RN

2:45 p.m. - 3:30 p.m. Treating Obesity: Is It Worth the Effort?
John D. Brunzell, MD

3:30 p.m. - 4:15 p.m. Break

4:15 p.m. - 5:00 p.m. Can Successful Long Term Weight Loss Be Predicted?
John Foreyt, PhD

5:00 p.m. - 5:45 p.m. Is Diet-Induced Weight Cycling a Health Risk?
Robert Jeffery, PhD

Track II

SATURDAY, JANUARY 23, 1993

SESSION 3: ***Individualized Educational and Counselling Strategies for Various Ethnic Populations***

CHAIR: *Deborah Hinnen, RN, MN, CDE*

8:30 a.m. - 9:15 a.m. Does Counselling Really Improve Compliance?
Duncan Wigg, PhD

9:15 a.m. - 10:00 a.m. Educating the Low Literacy Client
Deborah Hinnen, RN, MN, CDE

10:00 a.m. - 11:00 a.m. Break

11:00 a.m. - 11:45 a.m. Cultural and Ethnic Issues Impacting Health
James R. Gavin, III, MD, PhD

11:45 a.m. - 12:30 p.m. Barriers to Effective Nutrition Education: Clinical and Community Approaches
Brenda Broussard, RD, MPH

SUNDAY, JANUARY 24, 1993

SESSION 4: ***The Effects of Standards of Practice on the Delivery of Diabetes Health Care***

CHAIR: *Elizabeth Warren-Boulton, RN, MSN, CDE*

8:30 a.m. - 9:15 a.m. Standards for Medical Care
Larry Deeb, MD

9:15 a.m. - 10:00 a.m. Guidelines for Foot Care
Gayle E. Reiber, PhD

11:00 a.m. - 11:45 a.m. Guidelines for the Care of the Pregnant Diabetic Woman
John L. Kitzmiller, MD

10:00 a.m. - 11:00 a.m. Break

11:45 a.m. - 12:30 a.m. Standards for Patient Education
Elizabeth Warren-Boulton, RN, MSN, CDE

GENERAL INFORMATION

Exhibits

An exposition with over 30 companies will feature the most up-to-date products and services available for diabetes treatment. Time is included in the course program for attendees to visit the exhibits to review the latest developments in diabetes care. Morning coffee breaks will be served in the exhibit hall. NO ONE UNDER THE AGE 16 WILL BE PERMITTED IN THE EXHIBIT HALL.

Exhibit Hours:	Friday, January 22	10:00am - 2:00pm
	Saturday, January 23	10:00am - 2:00pm

Registration

Return the enclosed registration form with payment by check, money order, MasterCard, VISA or American Express to the American Diabetes Association. All checks and money orders must be payable in US funds and drawn on a US bank. Registration is not official until payment is received.

The registration fee (see schedule below) includes course materials and admission to all sessions, exhibits and social events. Registration will be confirmed if postmarked by December 28, 1992. Students, fellows and residents must include certification of status to obtain the reduced rate. Guest registration will admit individuals to the exhibit floor and social functions only.

Registration Fees

	Postmarked on or before December 4	Postmarked on or after December 5 or on-site
ADA Professional Member [MD]	$250	$300
Nonmember [MD]	$430	$500
ADA Professional Member [nonMD]	$165	$210
Nonmember [nonMD]	$250	$310
Student/Fellow/Resident	$125	$170
One Day Registration	$125	$125 Day
Guest Registration	$ 50	$ 50

One year membership to American Diabetes Association is included in the non-member fees. You may decline membership with American Diabetes Association; but you must still pay the non-member fee. A complete membership application will be mailed to you upon receipt of registration.

Cancellation Policy

All cancellation requests must be submitted in writing and postmarked on or before December 28, 1992. Cancellations postmarked before November 6 will receive a full refund less $50 processing fee. Cancellations postmarked between November 7 and December 28 will receive a registration refund less 50%. Cancellations postmarked after December 28, 1992 will not be honored.

Registration/Information Desk Hours

Thursday, January 21	4:00pm - 9:00pm
Friday, January 22	7:30am - 6:00pm
Saturday, January 23	7:30am - 5:00pm
Sunday, January 24	7:30am - 2:00pm

Program Objectives

AADE ADVANCED STUDIES INSTITUTE FOR DIABETES EDUCATION (ASIDE)

Courses from the American Association of Diabetes Educators' Advanced Studies Institute for Diabetes Education will again be offered in conjunction with the ADA Postgraduate Course. The Institute consists of a series of interrelated courses emphasizing experiential learning activities. Certain education and experience requirements must be met in order to be admitted to the Institute. Once admitted, candidates must successfully complete six core courses and six electives in areas which include diabetes education, complications, health care systems and settings, psychosocial, research, and business management.

The core course on Diabetes Complications and elective courses on "Teaching Patients with Low Literacy Skills" will be scheduled on free afternoons so as not to conflict with the Postgraduate sessions. Significant preparatory work must be completed prior to the onsite workshops and enrollment is limited to 32 students per course.

Further information about registration materials and deadlines for ASIDE are available ONLY from the AADE National Office, 444 North Michigan Avenue, Suite 1240, Chicago, Illinois 60611; telephone 1-800-338-DMED. The ASIDE fee is separate from the Postgraduate Course registration fee.

Accreditation

The American Diabetes Association is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

The American Diabetes Association is approved as a provider of continuing education in nursing by the Virginia Nurses' Association, which is accredited as an approver of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.

ADA also has applied to the American Dietetic Association and the American Association of Family Physicians for accreditation.

Credits will be distributed at the ADA Registration/ Information Desk between 12:30pm and 2:00pm on Sunday, January 24.

Preregistration Form

Please register only one person per form. This form can be copied for additional registrants.

Section A: Personal Data

Academic degree(s) ❑ MD ❑ DO ❑ PhD ❑ RN ❑ RD ❑ RPH ❑ Other _____

Please print or type all information clearly

First Name _____ MI_____ Last Name _____

Title _____ Affiliation _____

Mailing Address _____

City _____ State_____ Country _____ Zip Code _____

Business Phone Number _____ Business Fax Number _____

Specialty Area (check one)

❑ Adult Endocrinology
❑ Epidemiology
❑ Family Practice
❑ Geriatrics
❑ Internal Medicine
❑ Nursing
❑ Nutrition
❑ Opthalmology
❑ Ob/Gyn
❑ Pediatrics
❑ Pediatric Endocrinology
❑ Pharmacology
❑ Podiatry
❑ Psychology
❑ Public health
❑ Research
❑ Other (please indicate)

Type of Practice (check one)

❑ Clinic
❑ Corporate
❑ Hospital
❑ Private Practice
❑ Public Health
❑ HMO
❑ Research
❑ Academic
❑ Student
❑ Government/Military
❑ Other (please indicate)

Section B: Registration Fees

	Postmarked on or before December 4	Postmarked on or after December 5 or on site
ADA Professional Member (MD)	$250	$300
Nonmember (MD)	$430	$500
ADA Professional Member (non MD)	$165	$210
Nonmember (non MD)	$250	$310
Student/Fellow/Resident	$125	$170
One Day Registration	$125	$125

Indicate day that you will attend: _____

Guest Registration ..... $ 50 ..... $ 50

One year membership to ADA is included in the non-member fees. You may decline membership with ADA; but you must still pay the non-member fee. Please authorize that you would like to become a member of ADA by signing: _____

Cancellation Policy

All cancellation requests must be submitted in writing and postmarked on or before December 28, 1992. Cancellations postmarked before November 6 will receive a full refund less $50 processing fee. Cancellations postmarked between November 7 and December 28 will receive a registration refund less 50%. Cancellations postmarked after December 28, 1992 will not be honored.

Section C: Payment of Fees

Registration Fee $ _____

Method of Payment (Checks and money orders must be made payable to the American Diabetes Association and must be payable in US funds drawn on a US bank.) ❑ Check ❑ Money Order ❑ American Express ❑ VISA ❑ MasterCard

Card Issued in the name of: (please print) _____ Card Number _____ Expiration Date: _____
I authorize American Diabetes Association to charge the total payment fee indicated on this form to my credit card.

Signature: _____

Section D: Mailing Information

Please complete and return this form, with payment to: American Diabetes Association, Department 0825, McLean, VA 22109-0825
If you have questions regarding registration, please contact the ADA Meetings Department at (703) 549-1500 ext. 330
Fax number (703) 836-7439

For ADA Use only: Check No: _____ B/PCharge: _____ AMEX/VISA/MC _____ Amount Received: _____ Date Received: _____

The world's leading diabetes experts just wrote the only therapy manual you'll ever need.

Imagine not having to wade through volume after volume of diabetes therapy textbooks that consume too much of your time. Or having the expertise of more than 50 diabetes professionals at your fingertips in one new publication.

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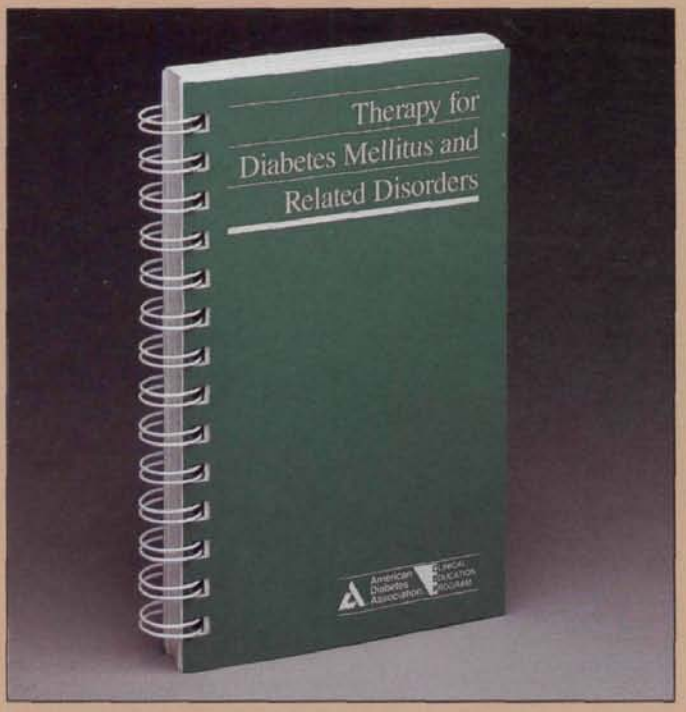

Therapy for Diabetes Mellitus and Related Disorders has just been published by the American Diabetes Association and is the authoritative guide to diabetes therapy. It's a "how to" reference manual filled with all the information you need to provide the best care for your patients. Yet each of the 49 chapters average just seven pages, so you'll be able to digest the latest in treatment and therapy in minutes.

You'll learn about:

- The latest drugs for treating diabetes, including sulfonylureas, metformin, and alpha-glucosidase inhibitors
- Genetic counseling for type I diabetes
- Treating diabetic nerve, eye, and kidney disease
- Controlling blood lipid abnormalities in diabetic patients
- Managing diabetic ketoacidosis and hyperglycemic hyperosmolar coma
- Much, much more!

Therapy for Diabetes Mellitus is also filled with more than 170 charts and tables, making each chapter easier to read and understand. Also, the manual's pocket-sized format will allow you to carry it with you for quick reference whenever necessary.

So order your copy of *Therapy for Diabetes Mellitus and Related Disorders* today. And put the most comprehensive and easy-to-use therapy manual in your pocket.

Yes! Please send me _____ copies of *Therapy for Diabetes Mellitus and Related Disorders* at $22.45 for members or $24.95 for nonmembers. I will be sure to add shipping and handling using the chart below.

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Allow 6-8 weeks for delivery. Add $3.00 to shipping & handling for each additional shipping address. Foreign orders must be paid in U.S. funds, drawn on a U.S. bank. Prices subject to change without notice.

DEADLINE FOR RECEIPT OF ABSTRACTS IS JANUARY 8, 1993

American Diabetes Association.

53rd SCIENTIFIC SESSIONS

12 - 15 June 1993 Las Vegas, Nevada

INSTRUCTIONS FOR PREPARATION OF ABSTRACTS

1. **Originality of work, adequacy of data, and clarity of exposition are the determinants in the selection of abstracts.** Make abstracts as informative as possible, including a brief statement of the purpose of the study or why it was done, the methods or what was done, the results observed, and the author's conclusions based on the results. Actual data should be summarized. It is inadequate to state "The results will be discussed" or "The data will be presented." Tables may be used to present data.

2. **Abstracts are not eligible for consideration if the paper has been presented at another national or international meeting, or will be published before ADA's Scientific Sessions.**

3. **The original abstract should be clear and within the border of the form, and is limited to the space provided.** If typed, use carbon ribbon or slightly used black silk ribbon. (New ribbons smudge; old one reproduce too faintly.) Practice typing the abstract in a rectangle 4 3/16" X 6 3/16" before using this form. An abstract printed by a laser printer or good-quality dot matrix printer is acceptable. However, the printed abstract must be an original copy and must be submitted on the abstract form. As with typed abstracts, the text must be within the border of the form. Those exceeding the border will not be accepted.

4. **The signature of an active member of the Professional Section of the American Diabetes Association is required to validate the abstract.** Members who sponsor non-members should verify that the latter are conforming to the rules.

5. **An individual (member or non-member) may only appear on two abstracts, and may appear as first author on only one abstract.** A member can appear as author, co-author, or sponsor. A non-member can appear as author or co-author.

6. **The final decision with respect to selection, programming, and/or publication of any abstract will be made by the Scientific Sessions Meeting Committee.**

7. **The original and three copies of the abstract must be provided.**

8. **Abstract headings must follow a specified format.** The format is:

a. Only the first letters of major words in the title should be capitalized. Do not use subtitles (e.g., Methods, Results) within the body of the abstract.

b. Author(s) complete first and last names should be listed and capitalized.

c. Author(s) who are members of ADA's Professional Section must be indicated by an asterisk.

d. Do not list degrees (e.g., MD, RN, RD) academic title(s), and institutional affiliation(s).

e. Include city and state or country of origin of work; do not include street address and zip code.

f. Headings should begin to the immediate right of the box located in the upper left corner of the abstract area.

Example:

☐ The Mechanism of Glucosamine-Induced Insulin Release, FRANZ M. MATSCHINSKY*, JANINA KOTLER-BRAJTBURG, JEANETTE ELLERMAN, and MARSHA ROGERS, St. Louis, MO

9. **The first line of the text of the abstract and the first line of any subsequent paragraphs should be indented three spaces.**

10. **The use of standard abbreviations is desirable.** Examples include kg, g, mg, ml, L (liter), meq, m (meter), mM (millimoles per liter), / (per), and % (percent). Place special or unusual abbreviations in parentheses after the full word the first time they appear. Use numerals to indicate numbers, except to begin sentences.

11. **Nonproprietary (generic) names should be used the first time a drug is mentioned and typed in lowercase letters; the first initial of a proper name is capitalized, e.g., aspirin (Bufferin).**

12. **Simple tables or special symbols may be included if they fit within the rectangular form provided.** Material that cannot be typed should be drawn in India ink.

13. **Do not fold the Abstract Form or copies.** They should be mailed with cardboard backing FIRST CLASS, or AIR MAIL when applicable, and addressed as follows:

Scientific Sessions Meeting Committee
American Diabetes Association
P.O. Box 26427
Alexandria, VA 22313-6427

14. **Changes to abstracts may not be made after submission.** Accepted abstracts will be printed as submitted. They should be carefully written and edited before submission.

15. **Abstracts must be received at the National Center by January 8, 1993.** Abstracts received after the deadline, regardless of the postmark date, will not be accepted.

16. **Provide one typed 3" X 5" white index card for each author named on the abstract to be listed in the index of the program.**

The author's name and degree(s) should be typed in the top left corner of the card. The abstract category should be typed in the center of the card.

Example:

SMITH, Leslie E.*, MD, PhD
Category -- Lipids and Lipoproteins

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PREGNANCY WARNING: ACE inhibitors should be discontinued as soon as pregnancy is detected (see Warnings).

Evaluation of the hypertensive patient should always include assessment of renal function (see Dosage and Administration). Angioedema has been reported with ACE inhibitors, including ZESTRIL (see Warnings).

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BRIEF SUMMARY

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and death to the developing fetus. When pregnancy is detected, ZESTRIL should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

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INDICATIONS AND USAGE

ZESTRIL is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents.

In using ZESTRIL, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that ZESTRIL does not have a similar risk. (See WARNINGS.)

CONTRAINDICATIONS

ZESTRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor.

WARNINGS

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including ZESTRIL. In such cases, ZESTRIL should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, eg, subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway should be promptly provided. (See ADVERSE REACTIONS.)**

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of the use with ZESTRIL in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, Drug Interactions, and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of ZESTRIL and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of ZESTRIL are insufficient to show that ZESTRIL does not cause agranulocytosis at similar rates. Marketing experience has revealed rare cases of neutropenia and bone marrow depression in which a causal relationship to lisinopril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ZESTRIL as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, ZESTRIL should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Lisinopril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of lisinopril were seen in studies of pregnant rats, mice, and rabbits. On a mg/kg basis, the doses used were up to 625 times (in mice), 188 times (in rats), and 0.6 times (in rabbits) the maximum recommended human dose.

PRECAUTIONS

General

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ZESTRIL, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ZESTRIL and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ZESTRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of ZESTRIL and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.0% of patients with congestive heart failure. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ZESTRIL. (See Drug Interactions.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent, and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ZESTRIL may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of ZESTRIL. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned to report light-headedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physicians.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physicians.

Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with ZESTRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Hypotension — Patients on Diuretic Therapy: Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ZESTRIL. The possibility of hypotensive effects with ZESTRIL can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ZESTRIL. If it is necessary to continue the diuretic, initiate therapy with ZESTRIL at a dose of 5 mg daily, and provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS, and DOSAGE AND ADMINISTRATION.) When a diuretic is added to the therapy of a patient receiving ZESTRIL, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic. (See DOSAGE AND ADMINISTRATION.)

Indomethacin: In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of ZESTRIL alone were compared to ZESTRIL given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant.

Other Agents: ZESTRIL has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No clinically important pharmacokinetic interactions occurred when ZESTRIL was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of ZESTRIL.

Agents Increasing Serum Potassium: ZESTRIL attenuates potassium loss caused by thiazide-type diuretics. Use of ZESTRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium with drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was usually reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if ZESTRIL is administered concomitantly with lithium.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 times* the maximum recommended daily human dose) or when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose).

*Based on patient weight of 50 kg.

Zestril® (lisinopril)

Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an in vitro alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an in vitro test in Chinese hamster ovary cells or in an in vivo study in mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril.

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters). See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers: Milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk caution should be exercised when ZESTRIL is given to a nursing mother.

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

ADVERSE REACTIONS

ZESTRIL has been found to be generally well tolerated in controlled clinical trials involving 2003 patients and subjects.

The most frequent clinical adverse experiences in controlled trials with ZESTRIL were dizziness (6.3%), headache (5.3%), fatigue (3.3%), diarrhea (3.2%), upper respiratory symptoms (3.0%), and cough (2.9%), all of which were more frequent than in placebo-treated patients. For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range.

For adverse experiences which occurred in more than 1% of patients and subjects treated with ZESTRIL or ZESTRIL plus hydrochlorothiazide in controlled clinical trials, comparative incidence data are listed in the table below.

	Percent of Patients in Controlled Studies		
	ZESTRIL (n = 2003†) Incidence (discontinuation)	ZESTRIL/Hydrochlorothiazide (n = 644) Incidence (discontinuation)	Placebo (n = 207) Incidence
Dizziness	6.3 (0.6)	9.0 (0.9)	1.9
Headache	5.3 (0.2)	4.3 (0.5)	1.9
Fatigue	3.3 (0.2)	3.9 (0.5)	1.0
Diarrhea	3.2 (0.3)	2.6 (0.3)	2.4
Upper Respiratory Symptoms	3.0 (0.0)	4.5 (0.0)	0.0
Cough	2.9 (0.4)	4.5 (0.8)	1.0
Nausea	2.3 (0.3)	2.5 (0.2)	2.4
Hypotension	1.8 (0.8)	1.6 (0.5)	0.5
Rash	1.5 (0.4)	1.6 (0.2)	0.5
Orthostatic Effects	1.4 (0.0)	3.4 (0.2)	1.0
Asthenia	1.3 (0.4)	2.0 (0.2)	1.0
Chest Pain	1.3 (0.1)	1.2 (0.2)	1.4
Vomiting	1.3 (0.2)	1.4 (0.0)	0.5
Dyspnea	1.1 (0.0)	0.5 (0.2)	1.4
Dyspepsia	1.0 (0.0)	1.9 (0.0)	0.0
Paresthesia	0.8 (0.0)	2.0 (0.2)	0.0
Impotence	0.7 (0.2)	1.6 (0.3)	0.0
Muscle Cramps	0.6 (0.0)	2.8 (0.6)	0.5
Back Pain	0.5 (0.0)	1.1 (0.0)	1.4
Nasal Congestion	0.3 (0.0)	1.2 (0.0)	0.0
Decreased Libido	0.2 (0.1)	1.2 (0.0)	0.0
Vertigo	0.1 (0.0)	1.1 (0.2)	0.0

†Includes 420 patients treated for congestive heart failure who were receiving concomitant digitalis and/or diuretic therapy.

Clinical adverse experiences occurring in 0.3% to 1.0% of patients in the controlled trials and rarer, serious, possibly drug related events reported in uncontrolled studies or marketing experience are listed below and, within each category, are in order of decreasing severity.

BODY AS A WHOLE: Chest discomfort, fever, flushing, malaise.

CARDIOVASCULAR: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension); angina pectoris, orthostatic hypotension, rhythm disturbances, tachycardia, peripheral edema, vasculitis, palpitation.

DIGESTIVE: Pancreatitis, hepatitis (hepatocellular or cholestatic jaundice), abdominal pain, anorexia, constipation, flatulence, dry mouth.

METABOLISM: Gout

MUSCULOSKELETAL: Joint pain, shoulder pain.

NERVOUS SYSTEM/PSYCHIATRIC: Depression, somnolence, insomnia, stroke, nervousness, confusion.

RESPIRATORY SYSTEM: Bronchitis, sinusitis, pharyngeal pain.

SKIN: Urticaria, pruritus, diaphoresis.

SPECIAL SENSES: Blurred vision.

UROGENITAL: Oliguria, progressive azotemia, acute renal failure, urinary tract infection.

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, and fever.

ANGIOEDEMA: Angioedema has been reported in patients receiving ZESTRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ZESTRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

HYPOTENSION: In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients. Hypotension or syncope was a cause of discontinuation of therapy in 0.5% of hypertensive patients. (See WARNINGS.)

In patients with congestive heart failure, hypotension occurred in 5.0% and syncope occurred in 1.0% of patients. These adverse experiences were causes for discontinuation of therapy in 1.3% of these patients.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Cough: See PRECAUTIONS - Cough

Clinical Laboratory Test Findings

Serum Electrolytes: Hyperkalemia. (See PRECAUTIONS.)

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0% of patients with essential hypertension treated with ZESTRIL alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. (See PRECAUTIONS.) Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 9.1% of patients with congestive heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g% and 1.3 vol%, respectively) occurred frequently in patients treated with ZESTRIL but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. In marketing experience, rare cases of neutropenia and bone marrow depression have been reported.

Overall, 2.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%), and serum potassium (0.4%).

OVERDOSAGE

The oral LD_{50} of lisinopril is greater than 20 g/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution.

Lisinopril can be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

Initial Therapy: In patients with uncomplicated essential hypertension not on diuretic therapy, the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20-40 mg per day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. Doses up to 80 mg have been used but do not appear to give greater effect. If blood pressure is not controlled with ZESTRIL alone, a low dose of a diuretic may be added. Hydrochlorothiazide, 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of ZESTRIL.

Diuretic Treated Patients: In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of ZESTRIL. The diuretic should be discontinued, if possible, for two to three days before beginning therapy with ZESTRIL to reduce the likelihood of hypotension. (See WARNINGS.) The dosage of ZESTRIL should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with ZESTRIL alone, diuretic therapy may be resumed as described above.

If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.)

Concomitant administration of ZESTRIL with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. (See PRECAUTIONS.)

Use in Elderly: In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of ZESTRIL. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution.

Dosage Adjustment in Renal Impairment: The usual dose of ZESTRIL (10 mg) is recommended for patients with creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≥ 10 mL/min ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 5 mg once daily. For patients with creatinine clearance < 10 mL/min (usually on hemodialysis) the recommended initial dose is 2.5 mg. *The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.*

Renal Status	Creatinine Clearance mL/min	Initial Dose mg/day
Normal Renal Function to Mild Impairment	> 30	10
Moderate to Severe Impairment	≥ 10 ≤ 30	5
Dialysis Patients	< 10	2.5††

††Dosage or dosing interval should be adjusted depending on the blood pressure response.

HOW SUPPLIED

5 mg Tablets (NDC 0038-0130) pink, capsule-shaped, biconvex, bisected, uncoated tablets, identified "ZESTRIL" on one side and "130" on the other side are supplied in bottles of 100 tablets and unit dose packages of 100 tablets.

10 mg Tablets (NDC 0038-0131) pink, round, biconvex, uncoated tablets identified "ZESTRIL 10" debossed on one side, and "131" debossed on the other side are supplied in bottles of 100 tablets and unit dose packages of 100 tablets.

20 mg Tablets (NDC 0038-0132) red, round, biconvex, uncoated tablets identified "ZESTRIL 20" debossed on one side, and "132" debossed on the other side are supplied in bottles of 100 tablets and unit dose packages of 100 tablets.

40 mg Tablets (NDC 0038-0134) yellow, round, biconvex, uncoated tablets identified "ZESTRIL 40" debossed on one side, and "134" debossed on the other side are supplied in bottles of 100 tablets and unit dose packages of 100 tablets.

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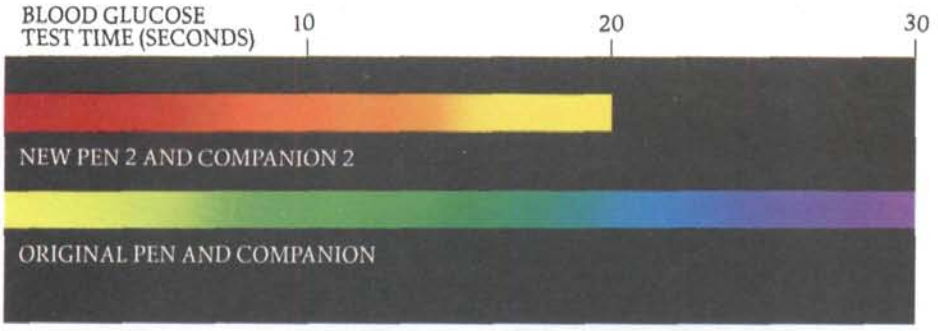

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There's no need to wipe or blot, saving time and reducing technique errors. No blood ever enters the sensor, eliminating the need for cleaning and the possibility of cross-contamination between samples. And calibration is a simple one-step process.

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Today, after years of research, testing, and refinement, MediSense can offer patients with diabetes even more:

For *increased ease of use,* the sensor starts automatically as soon as a small blood drop is applied to the Sensor Electrode. This eliminates the need for timing or "button-pushing" and further helps to reduce technique errors.

For *even faster test results,* we reduced the testing time from 30 seconds to *20 seconds,* making the quickest test on the market even quicker.

For *increased flexibility,* our assay reading range has been expanded to 20–600 mg/dL. And an added control feature compensates for temperature variances and eliminates interferences from uric acid and other substances in the blood.

NOTHING IS MORE CONVENIENT. EASY TO TEACH, EASY TO LEARN.

Only our sensors are so easy to learn (and teach), so fast to use, so simple to maintain, and so convenient to carry. And no other system offers a better combination of accuracy, speed, and convenience, with:

- The two smallest monitors available: the ingeniously designed Pen 2 and the credit-card sized Companion 2.
- Individually foil-wrapped, easily opened Sensor Electrodes, in packages of 25 and 50.

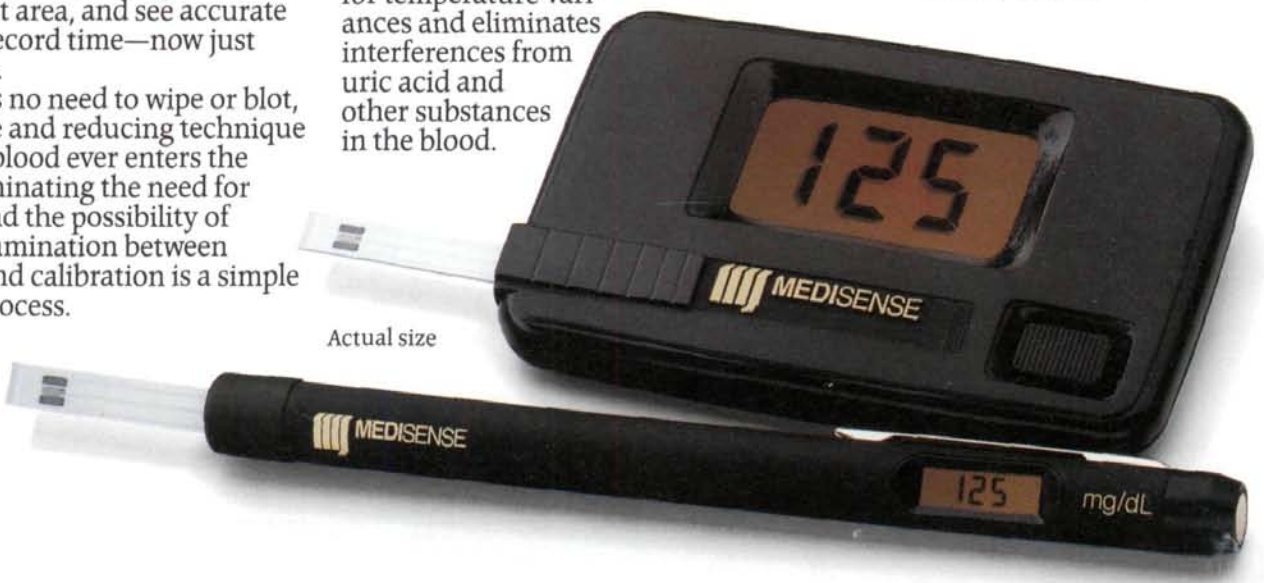
MEDISENSE SENSORS. THE BENEFITS ARE OBVIOUS. THE CHOICE IS SIMPLE.

For more information on the Pen 2 and Companion 2 Blood Glucose System, please call 1-800-537-3575.

No monitors are as discreet or test faster than MediSense Pen 2 and Companion 2 Sensors.

MEDISENSE

Sensors for a better life.



Actual size

Cambridge, MA 02139

From the Next Generation of rDNA Technology

NOVOLIN® 70/30

Novo Nordisk

Combining Control and Confidence

When it comes to glycemic CONTROL, the ideal insulin response is a natural one. NOVOLIN® 70/30 has been formulated to provide rapid onset with sustained duration for a more natural insulin profile than NPH alone.

When it comes to CONFIDENCE, you look for safety, accuracy, and convenience. NOVOLIN® 70/30 eliminates measuring and mixing errors and may improve patient adherence through a simple B.I.D. dosing regimen.

NOVOLIN® 70/30

Human Insulin

(recombinant DNA origin)

Combining Control and Confidence

For more information, call ***1-800-727-6500.***

WARNING: ANY CHANGE IN INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION.

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