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Diabetes Care

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Original Articles

Special Article

Editorial

Commentaries

American Diabetes Association.

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Treat hypertension at its source with...

ONCE-A-DAY

CARDURA®

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

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

Please see brief summary of prescribing information on adjacent page of this advertisement.

ONCE-A-DAY

CARDURA®

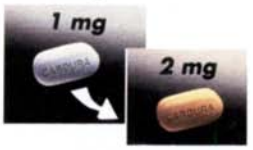
(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

Convenient once-a-day dosage

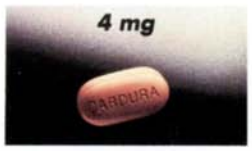
Most responsive patients are controlled with one daily dose of 4 to 8 mg[1]

—recommended initial dose is 1 mg, with dosage range of 1 mg to 16 mg per day.

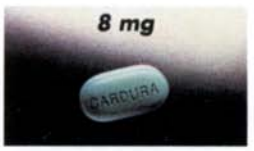
1 ***Begin all patients with CARDURA 1 mg once daily to minimize side effects. Evaluate supine and standing blood pressure. Prescribe CARDURA 2 mg once daily, if necessary.***



2 ***Evaluate for blood pressure control. Prescribe 4 mg once daily, if necessary.***



3 ***Evaluate for blood pressure control. Prescribe 8 mg once daily, if necessary. Maximum recommended dosage is 16 mg once daily.***



Reference: 1. Data available on request from Roerig.

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). 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

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 flashes, 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. 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.

65-4538-00-0 Issued Nov. 1990

Pfizer Roerig

A division of Pfizer Pharmaceuticals

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

VOLUME 15 NUMBER 2

Diabetes Care

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.

All manuscripts and other editorial correspondence should be sent by first class mail to Allan L. Drash, MD, Editor, *Diabetes Care*, Children's Hospital, Rangos Research Center, 3705 Fifth Avenue, Pittsburgh, PA 15213. Manuscripts and correspondence regarding review articles should be sent to Ralph A. DeFronzo, MD, Review Editor, *Diabetes Care*, Department of Medicine, Division of Diabetes, UT-HSCSA, 7703 Floyd Curl Drive, San Antonio, TX 78284.

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

Manuscripts should be prepared in accord with the requirements specified in the document "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," *Annals of Internal Medicine* 96:766–71, 1982. An "Instructions for Authors" page containing specifications for manuscript preparation appears in the January and July issues of each volume.

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American Diabetes Association.

Acceptance of Manuscripts on Diskette

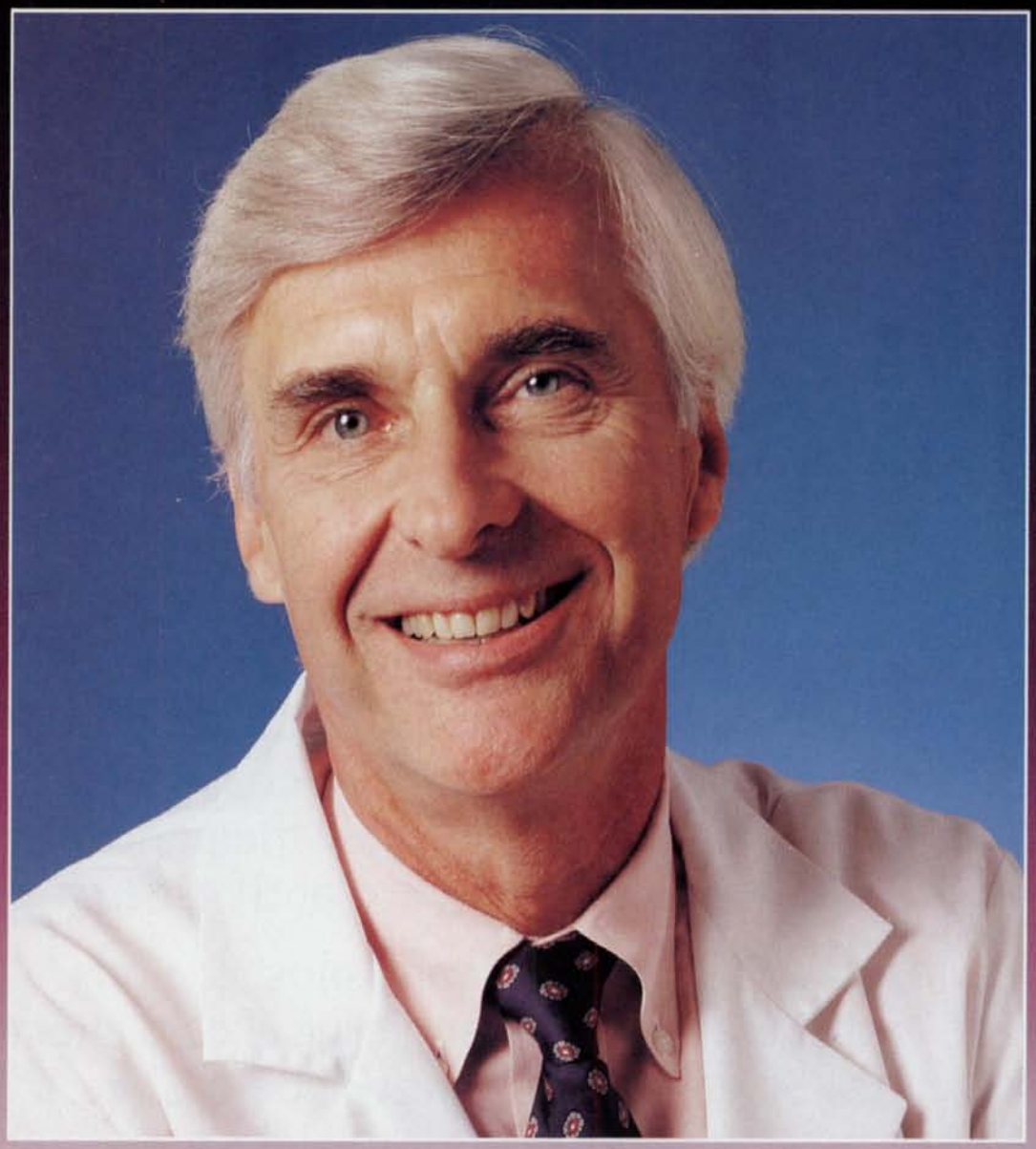
Diabetes Care welcomes the submission of manuscripts on computer diskettes beginning with the January 1992 issue. The text stored on diskettes can be used directly for typesetting, improving the efficiency and speed of journal production.

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 authors guidelines in the first issue of every volume.

Why are more and more doctors recommending B-D ULTRA-FINE™?



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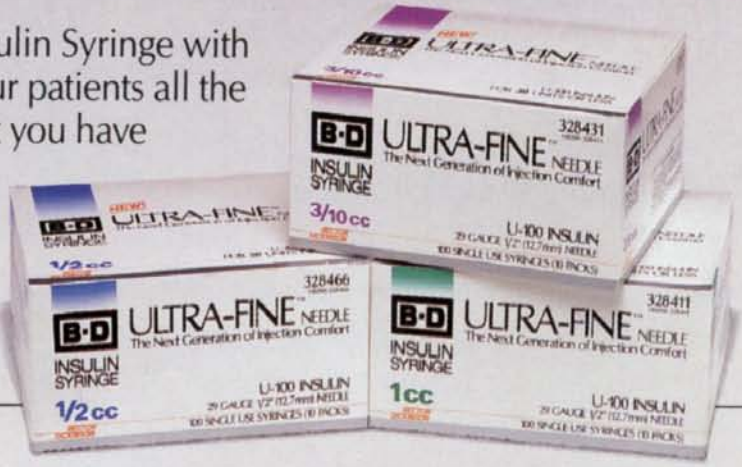

BETTER B-D DIABETES CARE

1992 52nd ANNUAL SCIENTIFIC SESSIONS

The American Diabetes Association and the 1992 Scientific Sessions Meeting Committee invite the participation of all professionals involved in diabetes research and in the delivery of diabetes care and services. Physicians, scientists, nurses, dietitians, administrators, and other health care professionals will benefit from the comprehensive programming and stimulating atmosphere. From the structured sessions to the exposition, participants will be challenged to update and review their knowledge in diabetes practice and research.

If the growing need for the latest and most exciting information in diabetes research and clinical care affects you, the **52nd Annual Scientific Sessions** will be the year's premier opportunity for your professional development.

Mark your calendar now for **June 20-23, 1992** in **SAN ANTONIO.**

LOCATION AND DATES

The Scientific Sessions and Exposition will be held in the San Antonio Convention Center.

The meeting opens 8:30 am Saturday, June 20 with symposia organized by ADA's Professional Section Councils and concludes 4:00 pm on Tuesday, June 23. The Awards Banquet will be held at the Marriott Rivercenter Hotel on Saturday.

NEW EXPANDED FORMAT

This year the number of program sessions has been increased by 75%! Expanded programming for clinical practice has been added to the dozens of lectures and hundreds of poster presentations on basic and clinical diabetes research.

Scientific Sessions Preliminary Program

Saturday, June 20, 1992

Professional Section Council Symposia Announced to Date Include:

Diabetes Complications: A Challenge for Behavioral Medicine

Macro and Microvascular Disease Complicating Pregnancy

Coping: An Experience with Diabetes Adherence **and** Health and Status in Diabetes: A Behavioral Challenge

Cardiovascular Complications in Diabetes

Role of Exercise and Physical Training in the Primary Prevention of Type II Diabetes

Therapeutic Strategies for Managing the Charcot Foot

Diabetic Renal Disease: Epidemiology, Clinical Advances, and Cost Considerations

Recent Public Policy Initiatives and the Practice of Clinical Endocrinology

Transgenic Animals and Targeted Gene Knockout as Tools of Diabetes Research

Sunday, June 21, 1992

Concurrent Symposia

Lifestyle Risk Factors as Complications of Diabetes

Gestational Diabetes Update

Cell Biology of Insulin Production & Secretion

Lipids and Obesity

Glucose Signalling in the Beta Cell

Insulin Regulation of Gene Expression

Quality Assurance of Diabetes Treatment

Exhibit Hall Open

Poster Session

President's Address

Banting Lecture

President's Poster Session

Monday, June 22, 1992

Concurrent Symposia

Variations of Diabetes in Minorities

Signal Relays

Role of Glucose & Hyperglycemia in the Complications of Diabetes

Clinical Implications of Exercise Therapy

New Technologies in Diabetes Therapy

New Approaches to Measuring *in vivo* Metabolism

Research Advances in the Mechanisms Regulating Glucose Transport

Diet Therapy in Diabetes

Exhibit Hall Open

Poster Session

Lilly Lecture

Tuesday, June 23, 1992

Symposium

Predicting and Preventing IDDM

Concurrent Symposia

Therapeutic Endpoints in Diabetes: How do we Measure Success?

Search for the Diabetes Gene(s)

Insulin Degradation

Exhibit Hall Open

Poster Session

CONTINUING EDUCATION

Continuing education credits for physicians (ACCME Category 1), nurses, and dietitians will be offered.

REGISTRATION INFORMATION

Contact the American Diabetes Association's Meetings Department to receive a complete Preliminary Program, housing information and a Registration Form. ***Take advantage of early registration discounts by completing and returning your Registration Form before March 15.***

For your insulin-mixing or NPH-using patients

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Rapid onset and sustained duration insulin activity in a single vial

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Axsain® Is Now **Zostrix®-HP**

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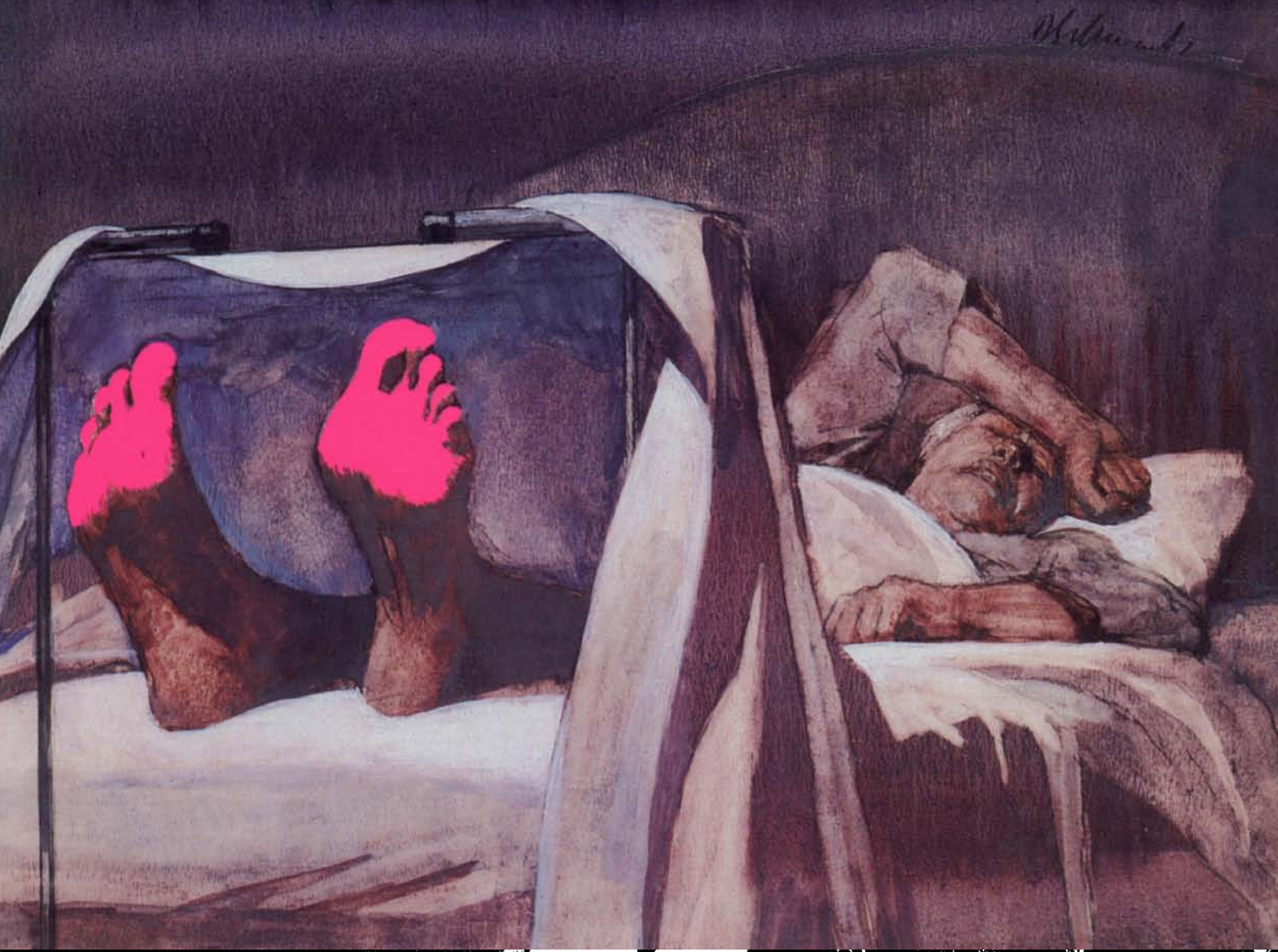
for peripheral neuropathies

Effective relief for the burning, throbbing, lancinating pain of diabetic neuropathy



Axsain® Is Now **Zostrix®-HP**

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(Capsaicin 0.075%) Cream

Unique topical therapy relieves pain of diabetic neuropathy

- **Topical, with no known systemic effects or drug interactions**
- **Pain selective; does not affect more discriminatory senses such as touch, pressure or vibration**
- **Patients applying Axsain three to four times daily report noticeable pain relief within two to four weeks**

Effective relief is achieved through proper patient use

Axsain should be rubbed into the skin in amounts sufficient to cover the area without resulting in a caked residue. If residue of dried material is left on the skin it may become airborne, which can cause coughing, sneezing and/or tearing.

A transient burning sensation and reddening of the skin may occur over the first several days of use. Application fewer than three times a day may not provide optimum pain relief and may cause the burning sensation to persist.

Illustrated, easy-to-read patient instruction booklets are included in every Axsain package.

Description: Axsain contains capsaicin 0.075% in an emollient cream base. Capsaicin is trans-8-methyl-N-vanillyl-6-nonenamide, a white crystalline powder with a molecular weight of 305.4. It is practically insoluble in water but very soluble in alcohol, ether and chloroform.

Active Ingredient: Capsaicin 0.075%

Inactive Ingredients: Benzyl Alcohol, Cetyl Alcohol, Glyceryl Monostearate, Isopropyl Myristate, Polyoxyethylene Stearate Blend, Purified Water, Sorbitol Solution, White Petrolatum

Actions and Indications: Current evidence suggests that Axsain works by its action on pain fibers and on a pain transmitting compound called substance P. The capsaicin in Axsain causes substance P to leave the nerve endings. With a lower amount of substance P in the nerve endings, pain impulses cannot be transmitted to the brain. Axsain is indicated for relief of neuralgias (pain from nerves near the surface of the skin) such as painful diabetic neuropathy and postsurgical pain.

Warnings: Avoid contact with eyes. Do not apply to wounds or damaged skin. Do not bandage tightly. Avoid inhaling airborne material from dried residue which can cause coughing, sneezing and/or tearing. If painful condition worsens or does not improve after 28 days, discontinue use of this product and consult your physician. Keep this and all drugs out of the reach of children.

Directions: Adults and children 2 years of age and older: Apply to affected area 3 to 4 times daily. A transient burning sensation related to the action of the product may occur over the first several days of use. Application schedules less than 3 times a day may not provide optimum pain relief and the burning sensation may persist. Wash hands immediately after application, avoiding areas where drug is applied.

How Supplied: 1.0 oz. tubes (NDC 57284-501-30) 2.0 oz. tubes (NDC 57284-501-60) U.S. Patent Nos. 4,486,450 and 4,536,404

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Glucotrol®

(glipizide) 5-mg and 10-mg Scored Tablets

When diet alone fails in non-insulin-dependent diabetes mellitus (NIDDM)

As with all sulfonylureas, hypoglycemia can occur.

Please see brief summary of GLUCOTROL® (glipizide) prescribing information on next page.

References: 1. Peterson CM, Sims RV, Jones RL, et al: Bioavailability of glipizide and its effect on blood glucose and insulin levels in patients with non-insulin-dependent diabetes. *Diabetes Care* 1982;5:497-500. 2. Goebel R, Leb G: Effects of glyburide and glipizide on levels of immunoreactive insulin and blood sugar, in *Glipizide: A Worldwide Review*. Princeton, NJ, Excerpta Medica, 1984, pp 9-15. 3. Reaven GM: Effect of glipizide treatment on various aspects of glucose, insulin, and lipid metabolism in patients with noninsulin-dependent diabetes mellitus. *Am J Med* 1983;75(November 30):8-14. 4. Berger W, Caduff F, Pasquel M, et al: The relative frequency of severe sulfonylurea hypoglycemia in the last 25 years in Switzerland. *Schweiz Med Wochenschr* 1986;116:145-151.

Brief Summary of Prescribing Information

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

CONTRAINDICATIONS: GLUCOTROL is contraindicated in patients with known hypersensitivity to the drug or with diabetic ketoacidosis, with or without coma, which should be treated with insulin.

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes*, 19, supp. 2:747-830, 1970). UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of GLUCOTROL 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: Renal and Hepatic Disease: The metabolism and excretion of GLUCOTROL may be slowed in patients with impaired renal and/or hepatic function. Hypoglycemia may be prolonged in such patients should it occur.

Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemia. Renal or hepatic insufficiency may increase the risk of 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 or people taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of Control of Blood Glucose: A loss of control may occur in diabetic patients exposed to stress such as fever, trauma, infection or surgery. It may then be necessary to discontinue GLUCOTROL and administer insulin.

Laboratory Tests: Blood and urine glucose should be monitored periodically. Measurement of glycosylated hemoglobin may be useful.

Information for Patients: Patients should be informed of the potential risks and advantages of GLUCOTROL, of alternative modes of therapy, as well as the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. *In vitro* studies indicate that GLUCOTROL binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to a clinical situation. Certain drugs tend to produce hyperglycemia and may lead to loss of control, including the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: *A 20-month study in rats and an 18-month study in mice at* doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

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

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. GLUCOTROL should be discontinued at least one month before the expected delivery date.

Nursing Mothers: Since some sulfonylurea drugs are known to be excreted in human milk, insulin therapy should be considered if nursing is to be continued.

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

ADVERSE REACTIONS: In controlled studies, the frequency of serious adverse reactions reported was very low. Of 702 patients, 11.8% reported adverse reactions and in only 1.5% was GLUCOTROL discontinued.

Hypoglycemia: *See PRECAUTIONS and OVERDOSAGE sections.*

Gastrointestinal: Gastrointestinal disturbances, the most common, were reported with the following approximate incidence: nausea and diarrhea, one in 70; constipation and gastralgia, one in 100. They appear to be dose-related and may disappear on division or reduction of dosage. Cholestatic jaundice may occur rarely with sulfonylureas: GLUCOTROL should be discontinued if this occurs.

Dermatologic: Allergic skin reactions including erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about one in 70 patients. These may be transient and may disappear despite continued use of GLUCOTROL; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

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

Metabolic: Hepatic porphyria and disulfiram-like alcohol reactions have been reported with sulfonylureas. Clinical experience to date has shown that GLUCOTROL has an extremely low incidence of disulfiram-like reactions.

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

Miscellaneous: Dizziness, drowsiness, and headache have each been reported in about one in fifty patients treated with GLUCOTROL. They are usually transient and seldom require discontinuance of therapy.

OVERDOSAGE: Overdosage of sulfonylureas including GLUCOTROL can produce hypoglycemia. 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 since hypoglycemia may recur after apparent clinical recovery. Clearance of GLUCOTROL from plasma would be prolonged in persons with liver disease. Because of the extensive protein binding of GLUCOTROL, dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION: There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOTROL; in general, it should be given approximately 30 minutes before a meal to achieve the greatest reduction in postprandial hyperglycemia.

Initial Dose: *The recommended starting dose is 5 mg before breakfast. Geriatric patients or those with liver disease* may be started on 2.5 mg. Dosage adjustments should ordinarily be in increments of 2.5-5 mg, as determined by blood glucose response. At least several days should elapse between titration steps.

Maximum Dose: The maximum recommended total daily dose is 40 mg.

Maintenance: Some patients may be effectively controlled on a once-a-day regimen, while others show better response with divided dosing. Total daily doses above 15 mg should ordinarily be divided.

HOW SUPPLIED: GLUCOTROL is available as white, dye-free, scored, diamond-shaped tablets imprinted as follows: 5 mg tablet—Pfizer 411 (NDC 5 mg 0049-4110-66) Bottles of 100; 10 mg tablet—Pfizer 412 (NDC 10 mg 0049-4120-66) Bottles of 100.

CAUTION: Federal law prohibits dispensing without prescription.

More detailed professional information available on request.

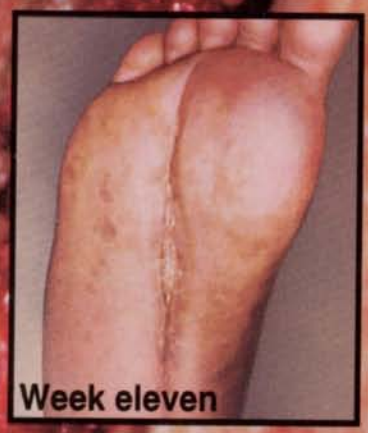
Pfizer

Roerig

Right foot, plantar surface of a 45-year-old male with diabetes.

Week one

A complete treatment program for chronic diabetic foot wounds



Week eleven

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Please see adjacent page for brief summary of prescribing information.

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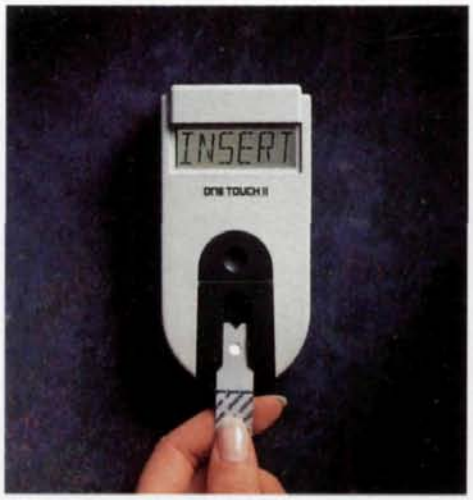
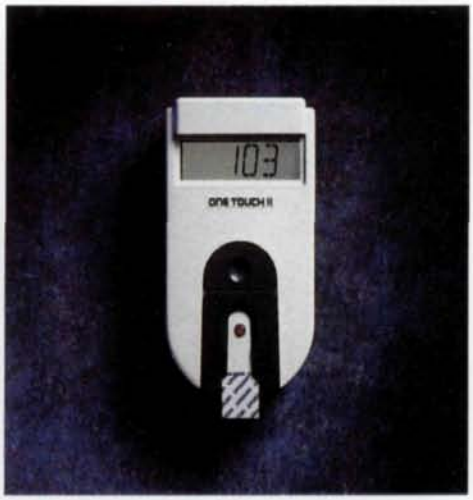


Press power, insert strip.

Apply sample. No wiping. No timing.



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Recent studies emphasize the need for consistent glucose control to reduce the risk of diabetic complications. Now RoTAG results can be used with confidence to optimize the therapeutic regimen and the frequency of follow-up and counseling.

Guidelines for Interpretation

Glucose	RoTAG	HbA_{1c}	Interpretation
—	—	—	Normal or controlled diabetic
^	^	—	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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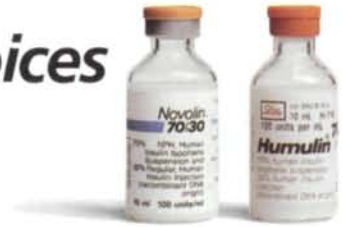

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