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Diabetes Care

FEBRUARY 1994

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American Diabetes Association.

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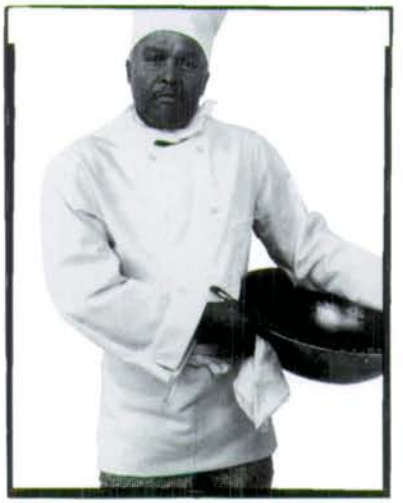
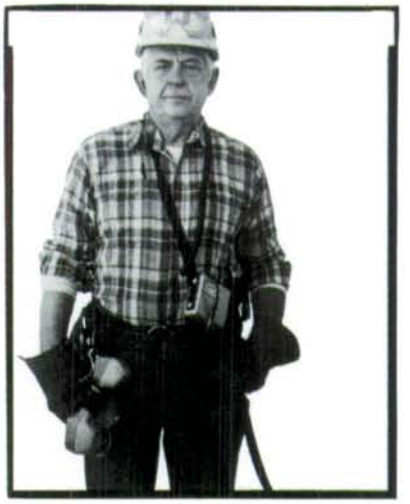


FOR TYPE II DIABETICS LIFE IS DEMANDING ENOUGH...





FOR TYPE II DIABETES,

TODAY'S LIFE DEMANDS INSULIN ON DEMAND

CAN'T ALWAYS EAT REGULARLY.

GLUCOTROL provides patients with insulin only when needed, responding on demand to meals and rising blood sugar[1]

DOUBLE SHIFTS.

GLUCOTROL, with insulin on demand, controls blood sugar quickly and effectively—all day and all night[1]

TOUGH PHYSICAL WORK.

GLUCOTROL works in response to meals; then insulin returns to near-normal levels once the meal challenge subsides[1,2]

When diet alone fails in NIDDM...

Glucotrol®

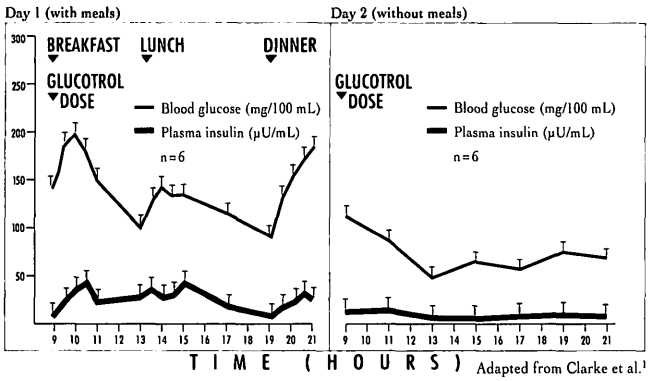
(glipizide) 5-mg and 10-mg Scored Tablets

As with all sulfonylureas, hypoglycemia may occur.

Pfizer Pratt

Please see brief summary of prescribing information on last page.

INSULIN ON DEMAND RESPONDS TO MEALS— AND REMAINS AT BASAL LEVELS DURING FASTING



Adapted from Clarke et al.[1]

The effect of fasting on mean blood sugar and plasma insulin levels was measured in a 2-day study of six NIDDM patients whose blood sugar levels had been controlled by a single daily dose of 5 to 10 mg of GLUCOTROL. On the first day, patients were served three meals. On the second, they received no food. Patients received their usual dose of GLUCOTROL at the start of each day.[1]

REFERENCES: 1. Clarke BF, Corrall RJM, Azzopardi J, Bhalla IP, Fraser DM, Duncan LJP. Clinical observations on glipizide: efficacy, duration of activity, and safety. In: *Glipizide: A Worldwide Review.* Princeton, NJ: Excerpta Medica; 1984:234-247. **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; 1984:9-15.

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 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 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, some azoles, 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. The effect of concomitant administration of DIFLUCAN (fluconazole) and GLUCOTROL has been demonstrated in a placebo-controlled crossover study in normal volunteers. All subjects received GLUCOTROL alone and following treatment with 100 mg of DIFLUCAN as a single daily oral dose for 7 days. The mean percentage increase in the GLUCOTROL AUC after fluconazole administration was 56.9% (range: 35 to 81).

Carcinogenesis, Mutagenesis, Impairment of Fertility: A 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 tablets are white, dye-free, scored, diamond-shaped, and imprinted as follows:

5 mg—Pfizer 411; 10 mg—Pfizer 412.

5 mg Bottles: 100's (NDC 0049-4110-66), (NDC 59012-411-66); 500's (NDC 0049-4110-73), (NDC 59012-411-73); Unit Dose 100's (NDC 0049-4110-41), (NDC 59012-411-41).

10 mg Bottles: 100's (NDC 0049-4120-66), (NDC 59012-412-66); 500's (NDC 0049-4120-73), (NDC 59012-412-73); Unit Dose 100's (NDC 0049-4120-41), (NDC 59012-412-41).

***CAUTION:** Federal law prohibits dispensing without prescription.*

More detailed professional information available on request.

Revised Jan. 1993

GC158A93

Pfizer Pratt Pharmaceuticals

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VOLUME 17 NUMBER 2

Diabetes Care

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Diabetes Care is a journal for the health-care practitioner that is intended to increase knowledge, stimulate research, and promote better management of people with diabetes mellitus. To achieve these goals, the journal publishes original articles on human studies in the areas of epidemiology, clinical trials, behavioral medicine, nutrition, education, health-care delivery, medical economics, and clinical care. The journal also publishes clinically relevant review articles, clinical observations, letters to the editor, and public health/medical news or points of view. 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; (412) 692-5851. Manuscripts and correspondence regarding review articles should be sent to Ralph A. DeFronzo, MD, Editor, *Diabetes Reviews*, Department of Medicine, Division of Diabetes, UT-HSCSA, 7703 Floyd Curl Drive, San Antonio, TX 78284.

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Manuscripts should be prepared in accord with the requirements specified in the document "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," *New England Journal of Medicine* 324:424–428, 1991. "Instructions for Authors" containing specifications for manuscript preparation appears in the January and July issues.

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(VOLUME 17, NUMBER 2)

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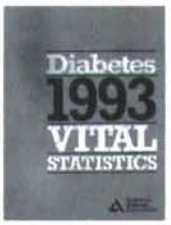
Diabetes: 1993 Vital Statistics

NEW!



Put the latest diabetes facts and figures right at your fingertips! Risk factors, treatment, prevention, and more...it's all right here with more than 40 charts and graphs to highlight important information. Perfect for the researcher, diabetes educator, or anyone interested in learning about diabetes and its complications. Softcover; 60pp. #PMDIVS93
Nonmember: $17.50; Member: $13.95

Medical Management of Pregnancy Complicated by Diabetes

NEW!

Comprehensive, yet concise! Takes you through every aspect of pregnancy and diabetes from prepregnancy counseling to postpartum follow-up and everything in between. Provides precise protocols for treatment of both pre-existing and gestational diabetes. A must-read! Softcover; 136 pp. #PMMPCD
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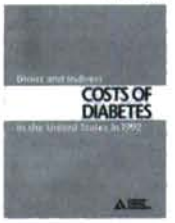
Direct and Indirect Costs of Diabetes in the U.S. in 1992

NEW!



Takes a hard look at the economic impact of diabetes on our nation. If $90 billion seems like a lot to you, then you need to get this book. That's how much diabetes cost this country in medical expenses and lost productivity from premature death and disability in a single year. Softcover; 32 pp.; #PMDIC92
Nonmember: $16.95; Member: $13.50

Therapy for Diabetes Mellitus and Related Disorders

Put the knowledge of more than 50 diabetes experts right at your fingertips! Contains the latest information on treating diabetes and its complications to help you provide the best care for your patients. And it's all presented in a concise, practical format so you can access information quickly and easily. Softcover; 368pp.; #PMTDRD
Nonmember: $34.50; Member: $27.50

Cardiovascular Risk Management: A Lecture Program

NEW!

This 3-hour program focuses on diabetes and its complications as risk factors for atherosclerotic vascular disease. Covers epidemiology, pathophysiology, assessment, and treatment for each risk factor. Includes case study discussion and presenter's script. 97 slides. #PMCEP3SS
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Nutrition Guide for Professionals

Nutrition plays a critical role in diabetes management and this guide will help you understand and effectively use meal planning in treating your diabetes patients. Emphasizes creation of individualized meal plans using the Exchange Lists for Meal Planning and alternative models. Softcover; 92 pp.; #PNNG
Nonmember: $12.95; Member: $11.00

Goals for Diabetes Education

Education is key in managing diabetes and this book provides you with a logical, thorough approach to the initial and in-depth phases of educating patients. Covers specific goals for each content area in a convenient checklist format. A must for any health care professional involved in treating patients with diabetes. Softcover; 48pp.; #PEGDE
Nonmember: $11.95; Member: $9.50

Diabetes and You: Hagase Responsable de su Salud—Spanish Video Series

Teach your spanish-speaking patients with these exciting educational videos! Set covers the risk to Latinos of developing diabetes, the importance of screening, and the consequences of late diagnosis. Includes four 8-12 minute videos, a leader's guide, and patient education materials. #PVIDSPSET
Nonmember: $69.95; Member: $54.95

Caring for Children with Diabetes

Teachers, school nurses, day-care providers, camp personnel—they all have responsibility for children, so when a child has diabetes, they need to know what's involved. This book will help them understand the disease and how to recognize and react to a diabetes emergency. Softcover; 16 pp. #PECARCH
Nonmember: $8.50; Member: $6.50

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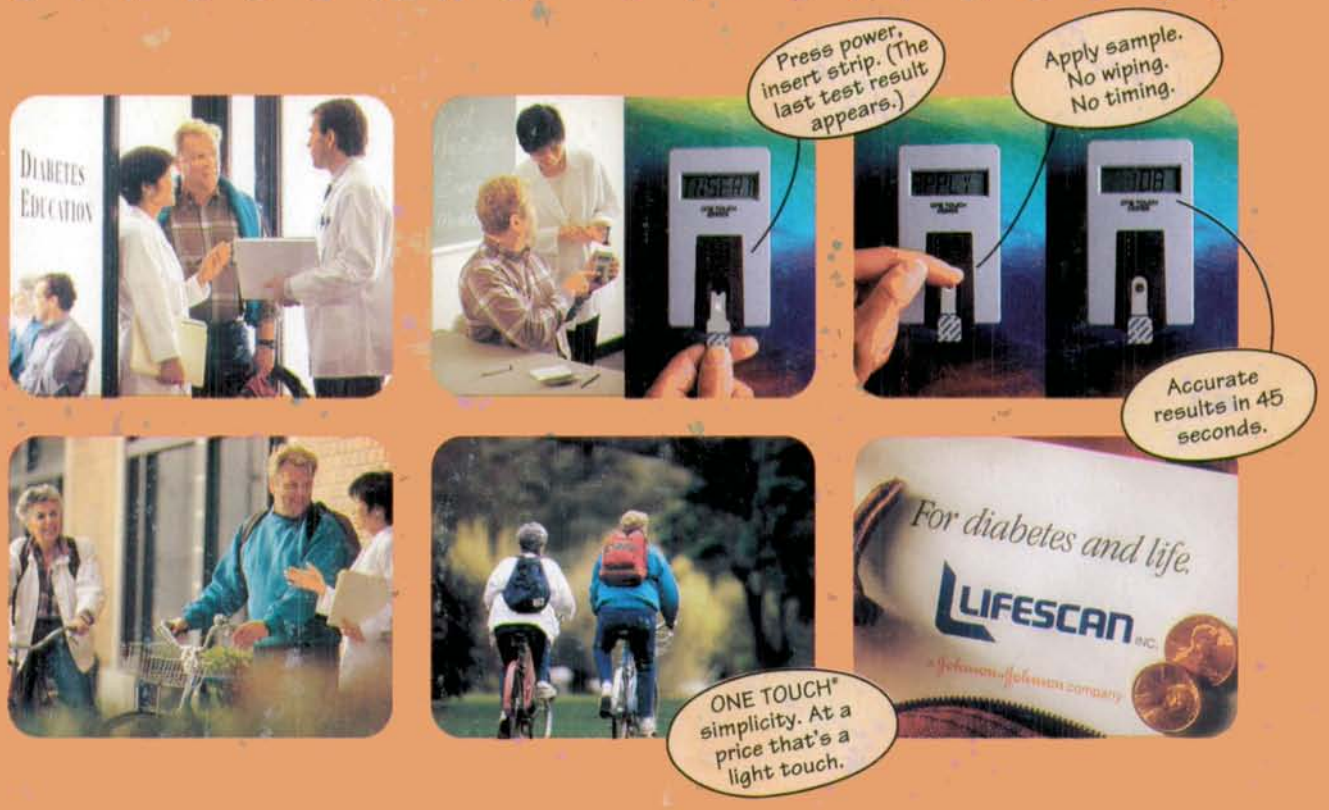

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*Data on file.
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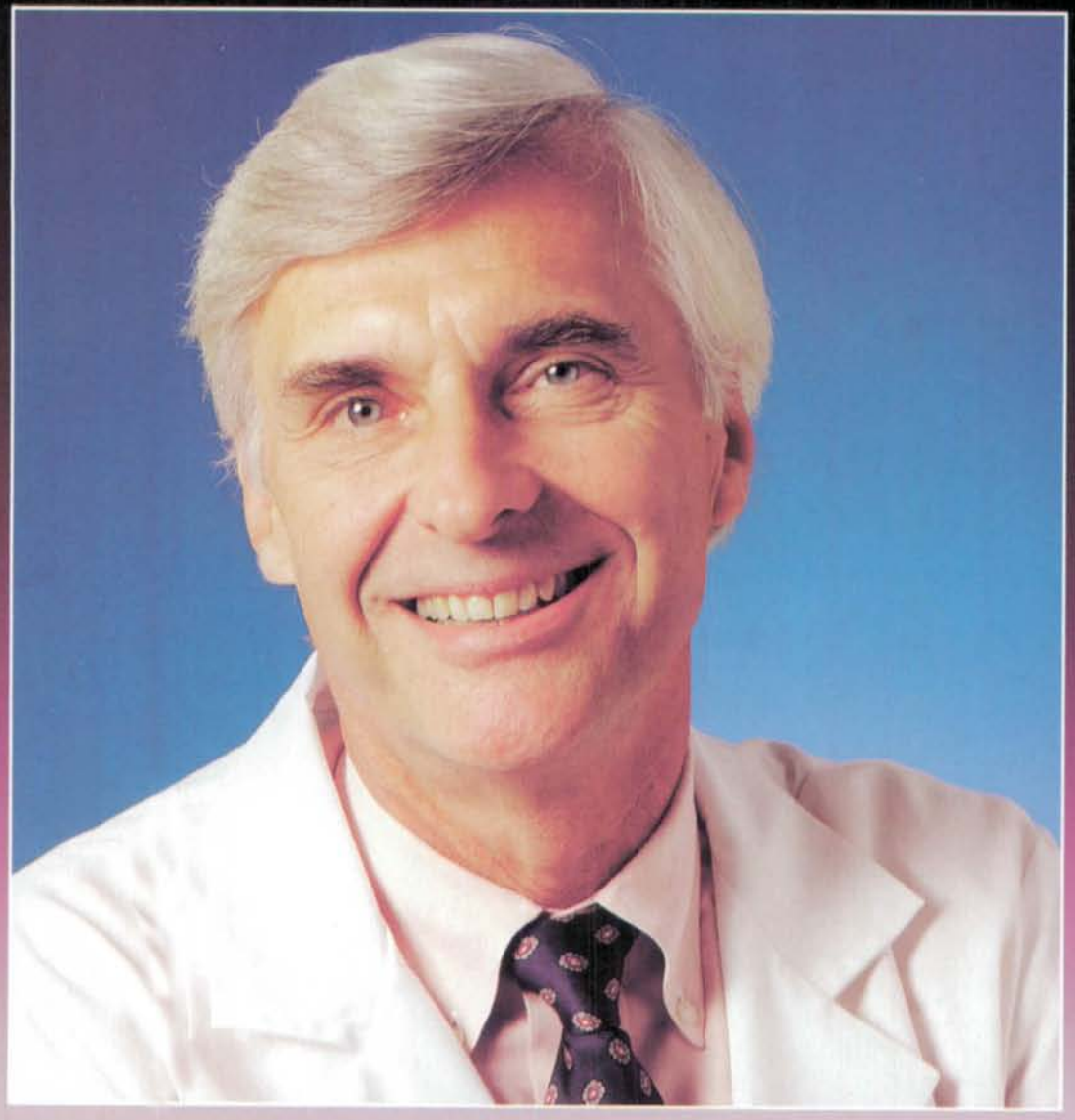

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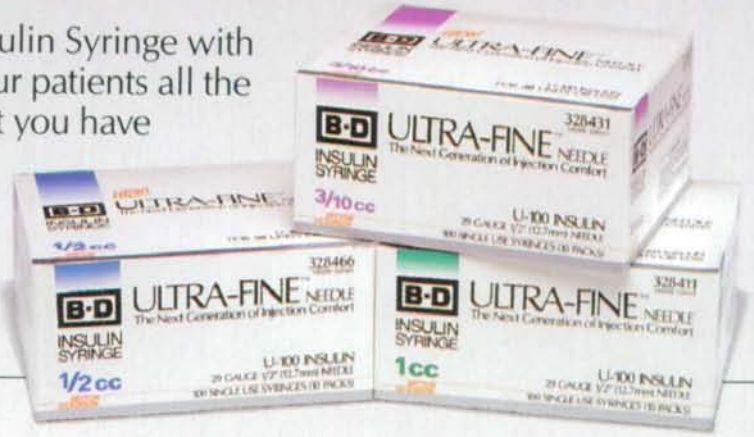
The ultra-comfortable B-D Insulin Syringe with the ULTRA-FINE™ Needle gives your patients all the quality, accuracy, ease and comfort you have come to expect from B-D. Plus the thinnest syringe needle ever.

The next generation of injection comfort.



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Novo Nordisk

Combining Control and Confidence

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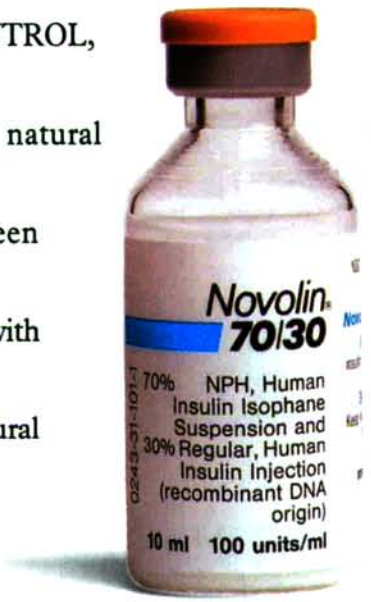

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NOVOLIN® 70/30

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.

205-62 May 1992 Printed in U.S.A.

Last week, all your patients with diabetes...

never missed a blood glucose reading...

always ate what they should...

and exercised every day.

Right?

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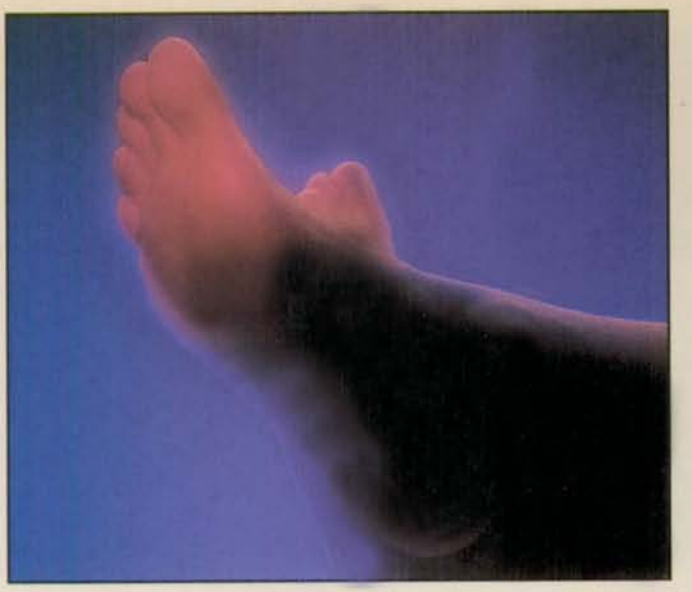

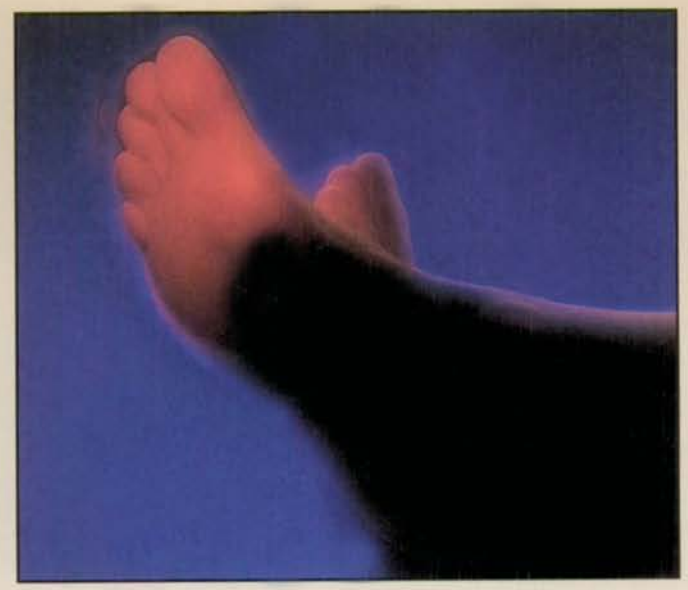

Proven efficacy • • • • •

■ 7 out of 10 patients treated with Zostrix®-HP (Capsaicin 0.075%) can expect significant pain relief[1]

Description: Zostrix/Zostrix-HP contain capsaicin in an emollient base containing benzyl alcohol, cetyl alcohol, glyceryl monostearate, isopropyl myristate, polyoxyethylene stearate blend, purified water, sorbitol solution and white petrolatum. Capsaicin is a naturally occurring substance derived from plants of the Solanaceae family with the chemical name trans-8-methyl-N-vanillyl-6-nonenamide. Capsaicin is 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.

Action: Although the precise mechanism of action of capsaicin is not fully understood, current evidence suggests that capsaicin renders skin and joints insensitive to pain by depleting and preventing reaccumulation of substance P in peripheral sensory neurons. Substance P is thought to be the principal chemomediator of pain impulses from the periphery to the central nervous system. In addition, substance P has been shown to be released into joint tissues and activate inflammatory mediators involved with the pathogenesis of rheumatoid arthritis.

Indication: Zostrix/Zostrix-HP are indicated for the temporary relief of pain from rheumatoid arthritis, osteoarthritis and relief of neuralgias such as the pain following shingles (herpes zoster) or painful diabetic neuropathy.

Warnings: FOR EXTERNAL USE ONLY. Avoid contact with eyes and broken (open) or irritated skin. Do not bandage tightly. If 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.** In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately.

Directions: Adults and children 2 years of age and older: Apply Zostrix/Zostrix-HP to affected area 3 to 4 times daily. Transient burning may occur upon application, but generally disappears in several days. Application schedules of less than 3 to 4 times a day may not provide optimum pain relief and the burning sensation may persist. **Wash hands if possible after applying Zostrix/Zostrix-HP avoiding areas where drug was applied.**

How Supplied:
Zostrix
0.7 oz (20 g) tube (NDC 52761-552-20)
1.5 oz tube (NDC 52761-552-45)
3.0 oz tube (NDC 52761-552-85)
Zostrix-HP
1.0 oz tube (NDC 52761-501-30)
2.0 oz tube (NDC 52761-501-60)
Store at room temperature 15°-30°C (59°-86°F)
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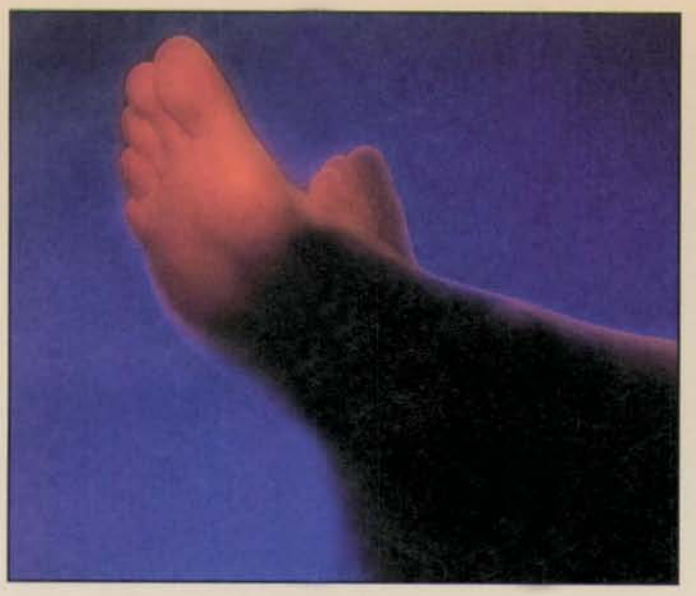

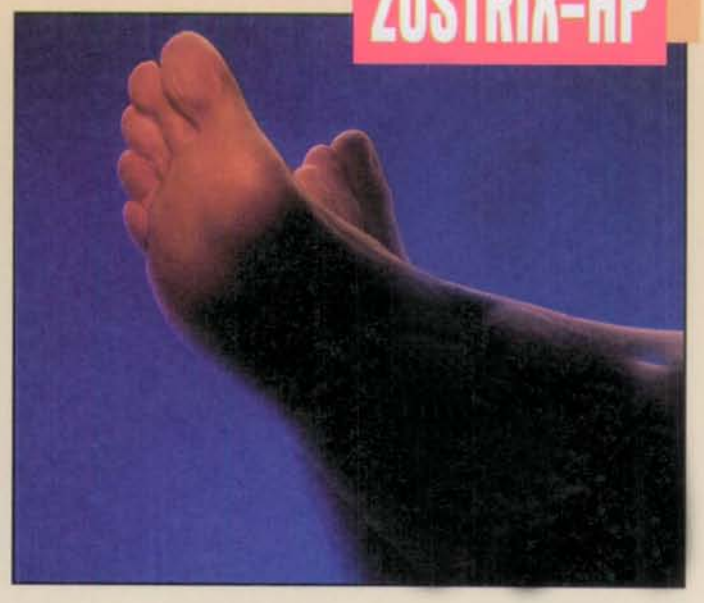

• without systemic side effects[1,2,3,4]

- No dizziness, drowsiness, headache or nausea
- No need for laboratory monitoring
- No drug interactions

REFERENCES

1. Donofrio P, Walker F, Hunt V, et al, The Capsaicin Study Group. Treatment of painful diabetic neuropathy with topical capsaicin: a multicenter, double-blind, vehicle-controlled study. *Arch Intern Med.* 1991; 151:2225-2229.
2. Tandan R, Lewis GA, Badger GB, Fries TJ. Topical capsaicin in painful diabetic neuropathy: effect on sensory function. *Diabetes Care.* 1992;15(1):15-18.
3. Tandan R, Lewis GA, Krusinski PB, Badger GB, Fries TJ. Topical capsaicin in painful diabetic neuropathy: controlled study with long-term follow-up. *Diabetes Care.* 1992;15(1):8-14.
4. Dailey GE, Muchmore DP, Springer JW, et al, The Capsaicin Study Group. Effect of treatment with capsaicin on daily activities of patients with painful diabetic neuropathy. *Diabetes Care.* 1992;15(2):159-165.

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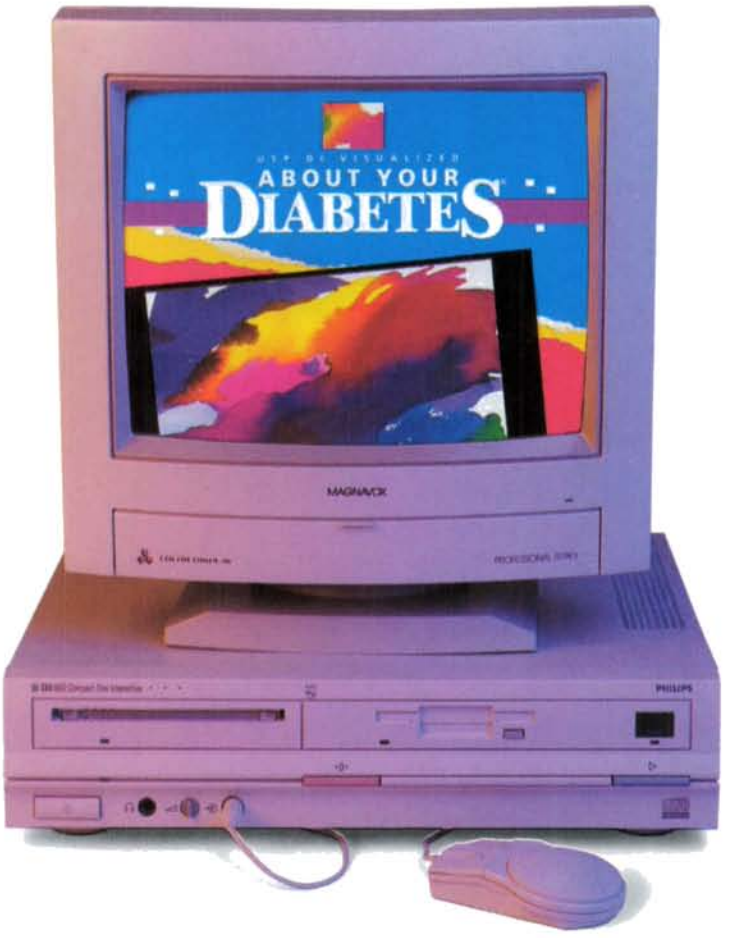

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Maximizing the Role of Nutrition in Diabetes Management

Overview

The American Diabetes Association, in cooperation with the Diabetes Care and Education Practice Group of The American Dietetic Association, has developed a continuing education program focusing on the role of nutrition in diabetes management. This program is directed toward health care professionals who serve the population with or at risk for diabetes. The program emphasizes the role of nutrition therapy in metabolic control of diabetes, and includes information obtained from the recently published DCCT (Diabetes Control and Complications Trial).

Target Audience

Dietitians, nurses and other health care professionals with an interest in the role of nutrition therapy in diabetes management.

Program

The full day program will include:

- DCCT: Nutrition Mandate
- Medical Framework for Nutrition Therapy
- Nutrition Research, Controversies and Applications for Clinical Practice
- Nutrition Therapy: A Blending of Sciences
- Diabetes Nutrition for Successful Outcomes in:
  - Long Term Care
  - Pregnancy: Gestational and Type I
  - The Medically Complicated Patient
  - Youth
- Nutrition Translation: Strategies for Success

Continuing Education Credits

Continuing education credits have been applied for through The American Dietetic Association.

Dates, Locations, and Information

This program is scheduled in twelve sites throughout the country from mid-March to mid-May 1994. For a list of sites, program information, or a registration form, contact Jill Thompson, Professional Programs Specialist, American Diabetes Association, 1660 Duke Street, Alexandria, VA 22314; phone: 800/232-3472 ext. 212; fax: 703/683-1839.

Registration Fee

The registration fee for this full day seminar is $50.00 which includes lunch, two coffee breaks, and participant materials.

This program is sponsored in part by an educational grant from Ross Products Division, Abbott Laboratories.

American Diabetes Association.

Diabetes Care and Education
A PRACTICE GROUP OF
THE AMERICAN DIETETIC ASSOCIATION
216 WEST JACKSON BOULEVARD
CHICAGO, ILLINOIS 60606-6995

ROSS PRODUCTS DIVISION
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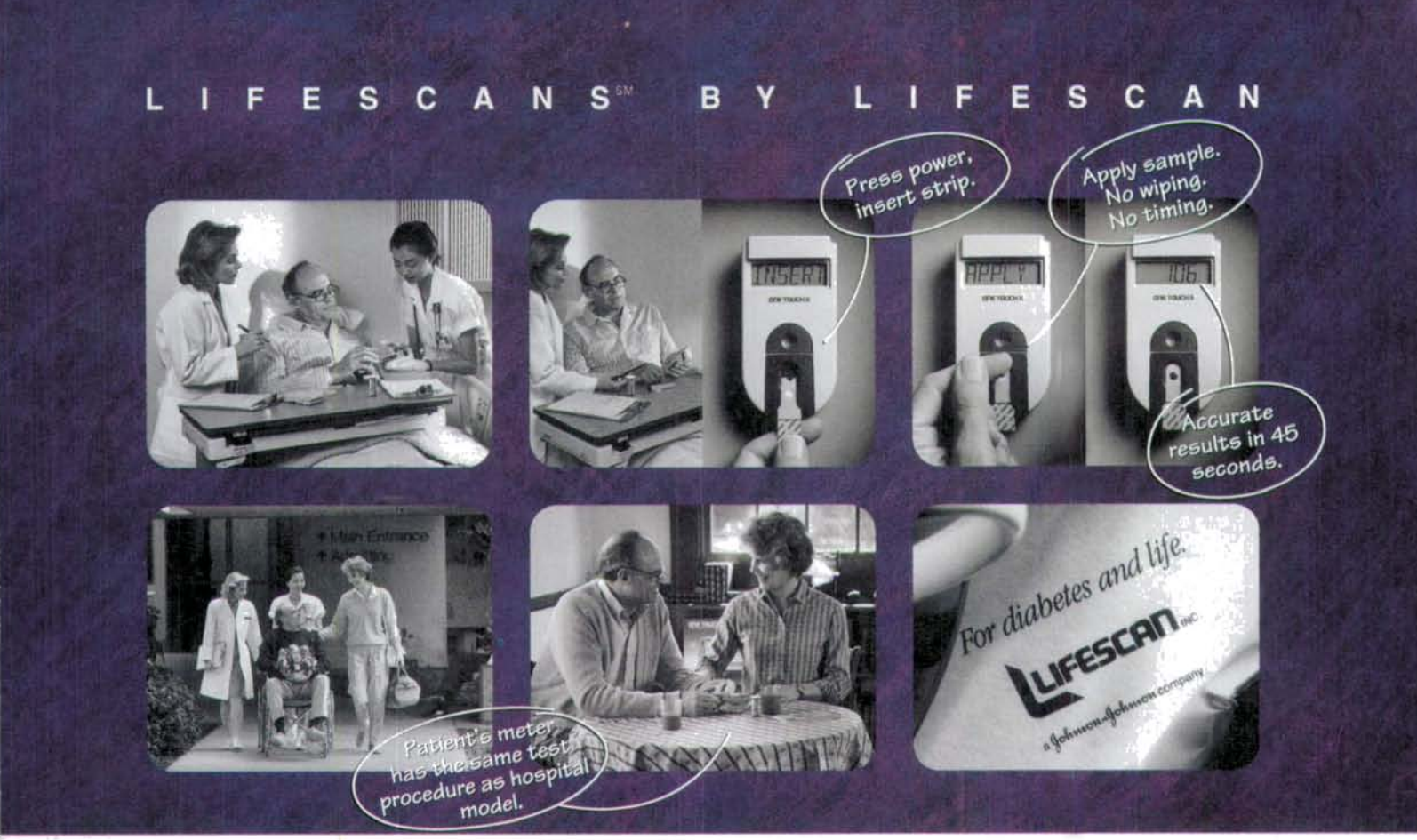
COLUMBUS, OHIO 43215-1724



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The Statistics are in...

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- Number of People with Diabetes
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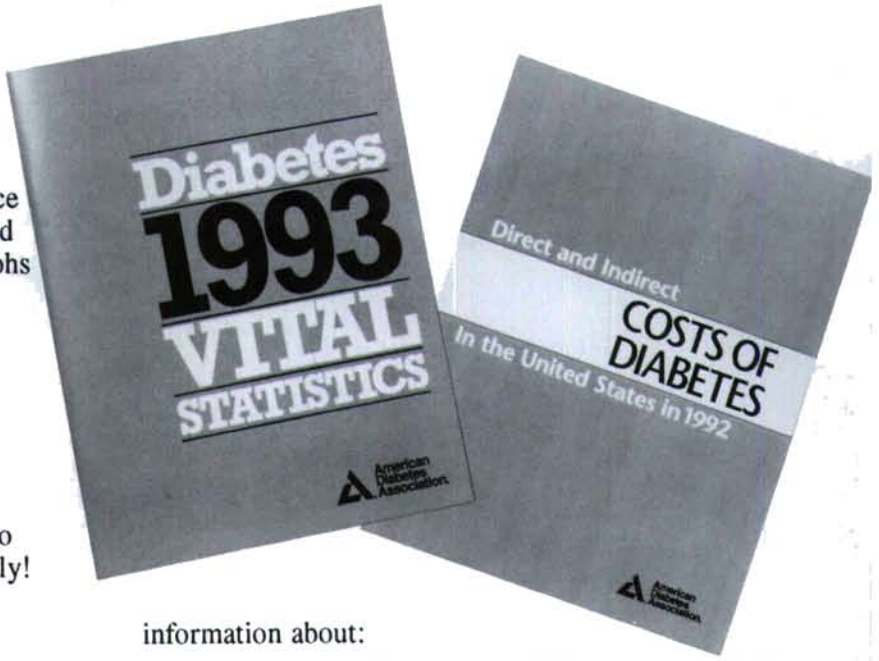
- Treatment
- Prevention
- Effect on Minorities

And it's all presented in an easy-to-use format so you can access nearly any statistic you need--instantly! It's perfect for the researcher, diabetes educator, or anyone interested in the most up-to-date findings on diabetes and its complications. Softcover, 60 pages, 1993.



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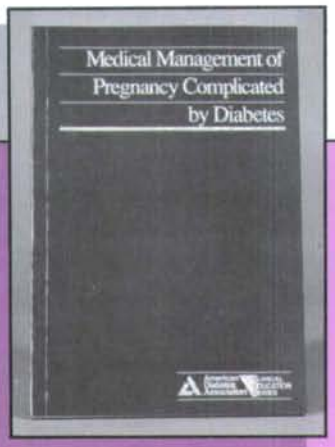

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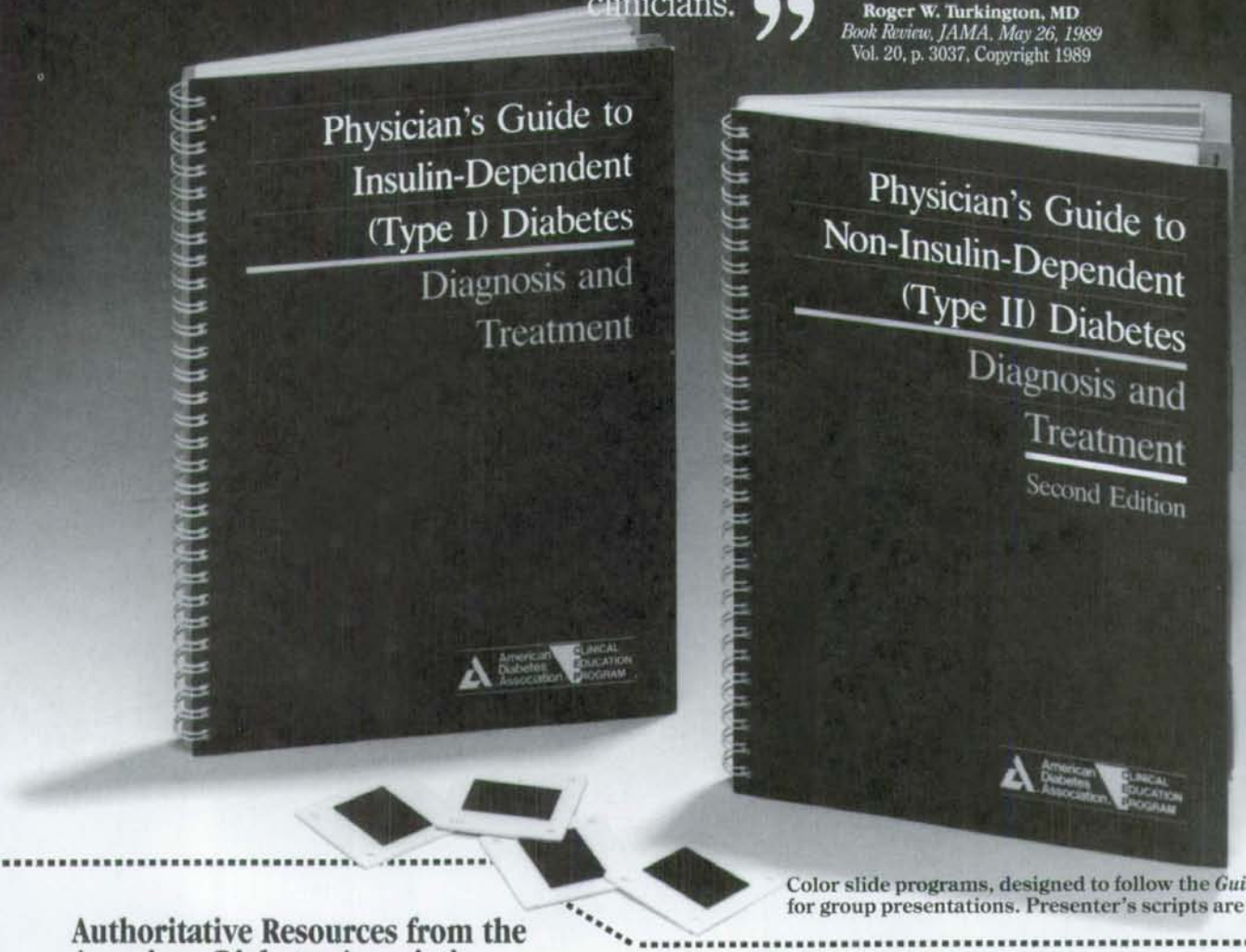

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CONTRAINDICATIONS: Known hypersensitivity reaction to nifedipine.
WARNINGS: Excessive Hypotension: Although in most angina patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine together with a beta-blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

The following information should be taken into account in those patients who are being treated for hypertension as well as angina.

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta Blocker Withdrawal: It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to those patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General—Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of nifedipine is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral Edema: Mild to moderate peripheral edema occurs in a dose dependent manner with an incidence ranging from approximately 10% to about 30% at the highest dose studied (180 mg). It is a localized phenomenon thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose angina or hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Other: As with any other non-deformable material, caution should be used when administering PROCARDIA XL in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of PROCARDIA XL.

Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small (5.4%) increase in mean alkaline phosphatase was noted in patients treated with PROCARDIA XL. This was an isolated finding not associated with clinical symptoms and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported. In controlled studies, PROCARDIA XL did not adversely affect serum uric acid, glucose, or cholesterol. Serum potassium was unchanged in patients receiving PROCARDIA XL in the absence of concomitant diuretic therapy, and slightly decreased in patients receiving concomitant diuretics.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs test with/without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions—Beta-adrenergic blocking agents: (See WARNINGS) Experience in over 1400 patients with Procardia® capsules in a noncomparative clinical trial has shown that concomitant administration of nifedipine and beta-blocking agents is usually well tolerated but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina.

Long Acting Nitrates: Nifedipine may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of nifedipine with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%), after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. The effect may be mediated by the known inhibition of cimetidine on hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats, for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats when given in doses 30 times the maximum recommended human dose. Nifedipine was embryotoxic (increased fetal resorptions, decreased fetal weight, increased stunted forms, increased fetal deaths, decreased neonatal survival) in rats, mice, and rabbits at doses of from 3 to 10 times the maximum recommended human dose. In pregnant monkeys, doses 2/3 and twice the maximum recommended human dose resulted in small placentas and underdeveloped chorionic villi. In rats, doses three times maximum human dose and higher caused prolongation of pregnancy. There are no adequate and well controlled studies in pregnant women. PROCARDIA XL® (nifedipine) Extended Release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE EXPERIENCES: Over 1000 patients from both controlled and open trials with PROCARDIA XL Extended Release Tablets in hypertension and angina were included in the evaluation of adverse experiences. All side effects reported during PROCARDIA XL Extended Release Tablet therapy were tabulated independent of their causal relation to medication. The most common side effect reported with PROCARDIA XL was edema which was dose related and ranged in frequency from approximately 10% to about 30% at the highest dose studied (180 mg). Other common adverse experiences reported in placebo-controlled trials include: headache (15.8%, compared to 9.8% placebo incidence); fatigue (5.9%, compared to 4.1% placebo incidence); dizziness (4.1%, compared to 4.5% placebo incidence); constipation (3.3%, compared to 2.3% placebo incidence); and nausea (3.3%, compared to 1.9% placebo incidence). Of these, only edema and headache were more common in PROCARDIA XL patients than placebo patients.

The following adverse reactions occurred with an incidence of less than 3.0%. With the exception of leg cramps, the incidence of these side effects was similar to that of placebo alone: *body as a whole/systemic*: asthenia, flushing, pain; *cardiovascular*: palpitations; *central nervous system*: insomnia, nervousness, paresthesia, somnolence; *dermatologic*: pruritus, rash; *gastrointestinal*: abdominal pain, diarrhea, dry mouth, dyspepsia, flatulence; *musculoskeletal*: arthralgia, leg cramps; *respiratory*: chest pain (nonspecific), dyspnea; *urogenital*: impotence, polyuria.

Other adverse reactions were reported sporadically with an incidence of 1.0% or less. These include: *body as a whole/systemic*: face edema, fever, hot flashes, malaise, periorbital edema, rigors; *cardiovascular*: arrhythmia, hypotension, increased angina, tachycardia, syncope; *central nervous system*: anxiety, ataxia, decreased libido, depression, hypertonia, hypoesthesia, migraine, paroniria, tremor, vertigo; *dermatologic*: alopecia, increased sweating, urticaria, purpura; *gastrointestinal*: eructation, gastroesophageal reflux, gum hyperplasia, melena, vomiting, weight increase; *musculoskeletal*: back pain, gout, myalgias; *respiratory*: coughing, epistaxis, upper respiratory tract infection, respiratory disorder, sinusitis; *special senses*: abnormal lacrimation, abnormal vision, taste perversion, tinnitus; *urogenital/reproductive*: breast pain, dysuria, hematuria, nocturia.

Adverse experiences which occurred in less than 1 in 1000 patients cannot be distinguished from concurrent disease states or medications.

The following adverse experiences, reported in less than 1% of patients, occurred under conditions (e.g., open trials, marketing experience) where a causal relationship is uncertain: gastrointestinal irritation, gastrointestinal bleeding.

In multiple-dose U.S. and foreign controlled studies with nifedipine capsules in which adverse reactions were reported spontaneously, adverse effects were frequent but generally not serious and rarely required discontinuation of therapy or dosage adjustment. Most were expected consequences of the vasodilator effects of Procardia. Adverse experiences reported in placebo-controlled trials include: dizziness, lightheadedness, and giddiness (27%, compared to 15% placebo incidence); flushing, heat sensation (25%, compared to 8% placebo incidence); headache (23%, compared to 20% placebo incidence); weakness (12%, compared to 10% placebo incidence); nausea, heartburn (11%, compared to 8% placebo incidence); muscle cramps, tremor (8%, compared to 3% placebo incidence); peripheral edema (7%, compared to 1% placebo incidence); nervousness, mood changes (7%, compared to 4% placebo incidence); palpitation (7%, compared to 5% placebo incidence); dyspnea, cough, and wheezing (6%, compared to 3% placebo incidence); and nasal congestion, sore throat (6%, compared to 8% placebo incidence).

There is also a large uncontrolled experience in over 2100 patients in the United States. Most of the patients had vasospastic or resistant angina pectoris, and about half had concomitant treatment with beta-adrenergic blocking agents. The relatively common adverse events were similar in nature to those seen with PROCARDIA XL.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

In a subgroup of over 1000 patients receiving Procardia with concomitant beta blocker therapy, the pattern and incidence of adverse experiences was not different from that of the entire group of Procardia treated patients (See PRECAUTIONS.)

In a subgroup of approximately 250 patients with a diagnosis of congestive heart failure as well as angina, dizziness or lightheadedness, peripheral edema, headache or flushing each occurred in one in eight patients. Hypotension occurred in about one in 20 patients. Syncope occurred in approximately one patient in 250. Myocardial infarction or symptoms of congestive heart failure each occurred in about one patient in 15. Atrial or ventricular dysrhythmias each occurred in about one patient in 150.

In post-marketing experience, there have been rare reports of exfoliative dermatitis caused by nifedipine.

More detailed professional information available on request.

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