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Diabetes Care

MAY 1994

Original Articles

Short Reports

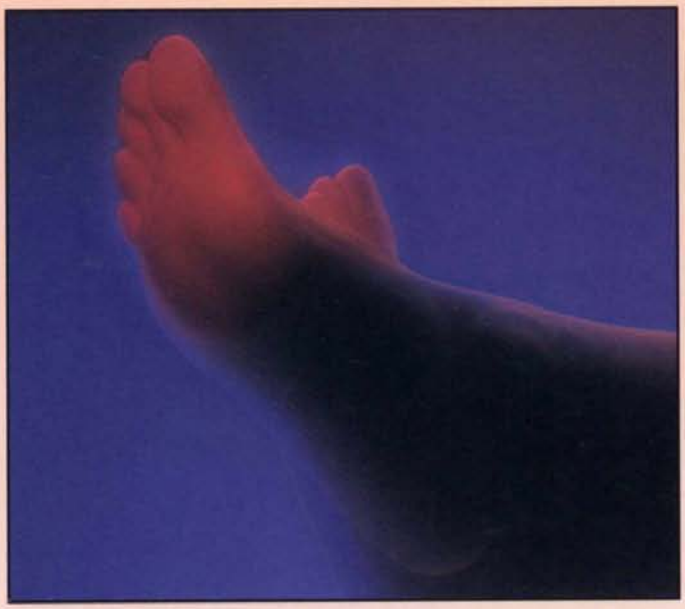
Commentaries

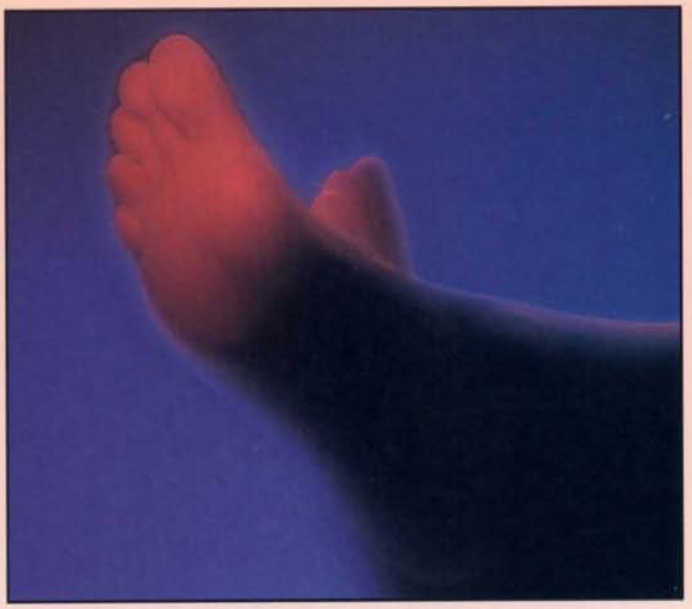
Technical Reviews and Position Statements

American Diabetes Association.

ISSN 0149-5992

Zostrix®-HP... For Burning, Throbbing, Of Diabetic





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)
U.S. Patent Nos. 4486450 and 4536404

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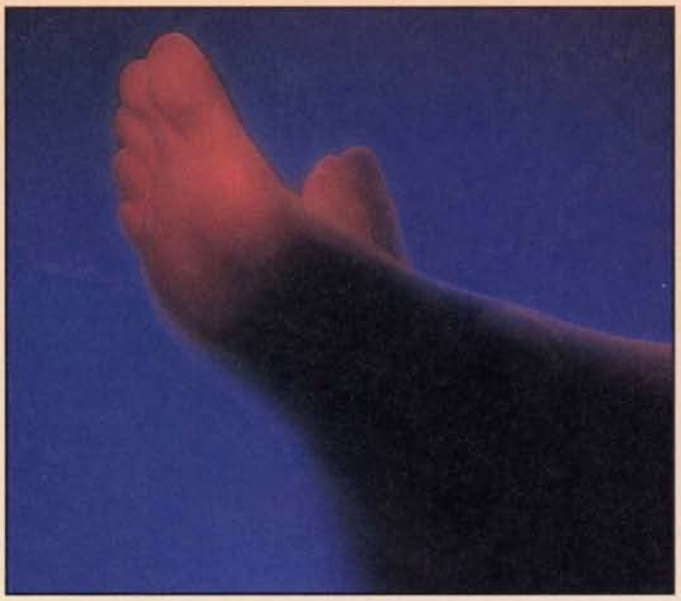

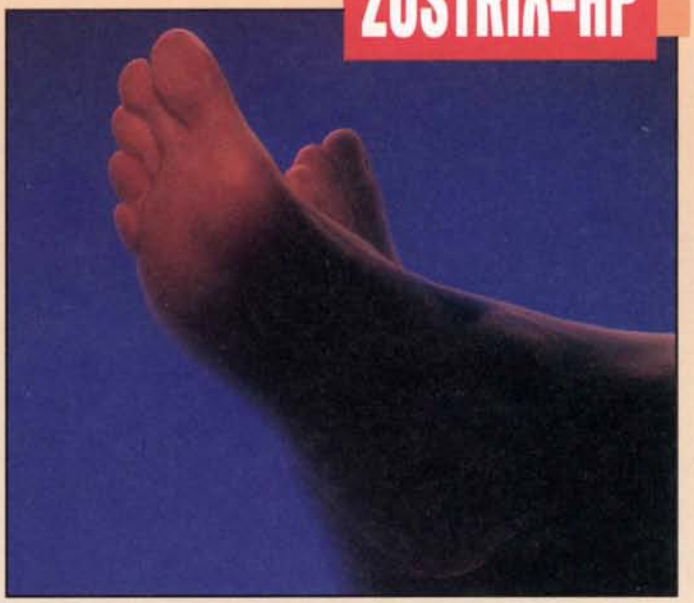

• without systemic side effects[1,2,3,4]

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

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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.
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Zostrix®-HP

(Capsaicin 0.075%)
Topical Analgesic Cream

Printed in U.S.A.

Z 6021 DRM-225D

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

VOLUME 17 NUMBER 5

Diabetes Care

Diabetes Care is a journal for the health-care practitioner that is intended to increase knowledge, stimulate research, and promote better management of people with diabetes 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 5)

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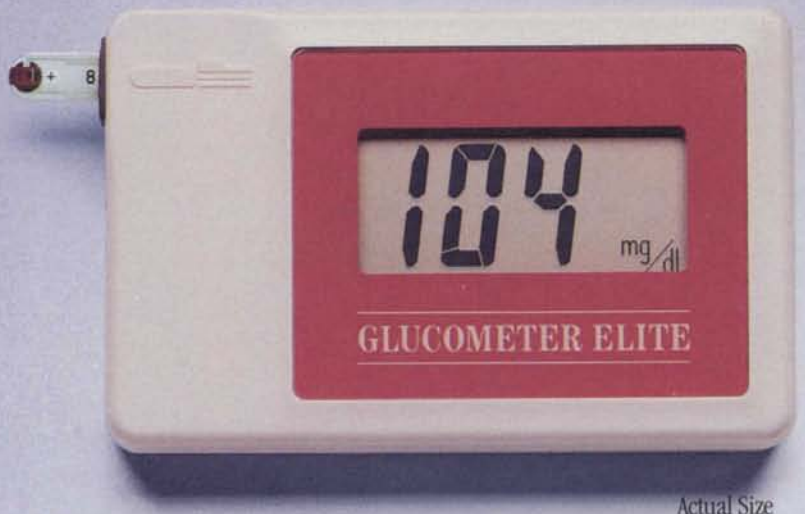

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*Consumer promotion effective March 1–June 30, 1994.

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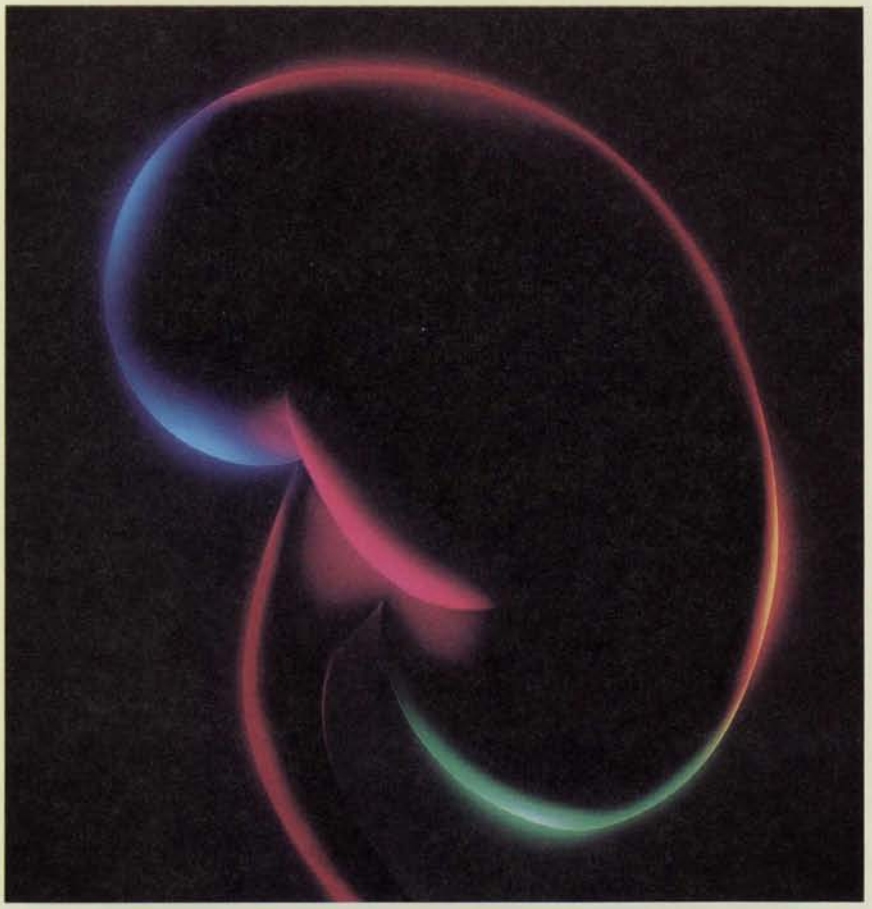
In type I IDDM patients with retinopathy*

NEW INDICATION
FOR DIABETIC NEPHROPATHY (PROTEINURIA >500 MG/DAY)



CAPOTEN®
(captopril)

12.5 mg, 25 mg, 50 mg, 100 mg Scored Tablets

*Insulin-dependent diabetes mellitus.

CAPOTEN is contraindicated in patients who are hypersensitive to this product. Angioedema has been reported in patients receiving ACE inhibitors.

Please see brief summary, including the **boxed WARNING regarding Use in Pregnancy,** on the last pages of this ad.


New Hope
"I've got this wonderful new lease on life now. I have a chance to keep my kidneys longer."
Beth G.
Actual study participant
USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, CAPOTEN should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

In type I IDDM patients with retinopathy

New indication for diabetic nephropathy (proteinuria >500 mg/day)

A 51% REDUCTION IN THE RISK OF END-STAGE RENAL DISEASE (DIALYSIS, RENAL TRANSPLANTATION) OR DEATH.

— CAPOTEN achieved these results in both normotensive and hypertensive type I IDDM patients – independent of blood pressure reduction alone.[1]

— CAPOTEN was well tolerated in this patient population. The most common causes for discontinuation included: dizziness/hypotension (2.4%), hyperkalemia (2.0%), GI disturbance (1.0%), rash (0.5%), and cough (0.5%).[2]

CAPOTEN® (captopril)

12.5 mg, 25 mg, 50 mg, 100 mg Scored Tablets

CAPOTEN is contraindicated in patients who are hypersensitive to this product. Angioedema has been reported in patients receiving ACE inhibitors.

Please see brief summary on the last pages of this ad.

New indication
for diabetic nephropathy (proteinuria >500 mg/day) in type I IDDM patients with retinopathy

The only drug therapy proven to slow the progression of diabetic kidney disease.

CAPOTEN® (captopril)

12.5 mg, 25 mg, 50 mg, 100 mg Scored Tablets

The recommended dosage of CAPOTEN for long-term use to treat diabetic nephropathy is 25 mg tid.

CAPOTEN® TABLETS
Captopril Tablets

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

CONTRAINDICATIONS: CAPOTEN (captopril) is contraindicated in patients who are hypersensitive to this product or any other angiotensin-converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

WARNINGS: Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Neutropenia/Agranulocytosis: Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7 percent of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of the reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75 percent received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13 percent of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately two-week intervals for about three months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course. **Proteinuria:** Total urinary proteins > 1 g per day were seen in about 0.7 percent of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (> 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in the proteinuric patients. **Hypotension:** Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in salt/volume depleted persons (such as those treated vigorously with diuretics), patients with heart failure or those patients undergoing renal dialysis. (See PRECAUTIONS: Drug Interactions.) In heart failure, where the blood pressure was either normal or low, transient

decreases in mean blood pressure > 20% were recorded in about half of the patients. This transient hypotension is more likely to occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased. **BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.** **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 captopril 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, captopril should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress 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 a means of reversing hypotension and/or substituting for disordered renal function. While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation. When captopril was given to rabbits at doses about 0.8 to 70 times (on a mg/kg basis) the maximum recommended human dose, low incidences of craniofacial malformations were seen. No teratogenic effects of captopril were seen in studies of pregnant rats and hamsters. On a mg/kg basis, the doses used were up to 150 times (in hamsters) and 625 times (in rats) the maximum recommended human dose. **Hepatic Failure:** Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

PRECAUTIONS: General: *Impaired Renal Function* — Hypertension — Some patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure — About 20% of patients develop stable elevations of BUN and serum creatinine > 20 % above normal or baseline upon long-term treatment. Less than 5% of patients, generally those with severe preexisting renal disease, required discontinuation of treatment due to progressively increasing creatinine. (See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS: Altered Laboratory Findings.) *Hyperkalemia:* Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. When treated with ACE inhibitors, patients at risk for the development of hyperkalemia include those with: renal insufficiency; diabetes mellitus; and those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or other drugs associated with increases in serum potassium. In a trial of type I diabetic patients with proteinuria, the incidence of withdrawal of treatment with captopril for hyperkalemia was 2% (4/207). In two trials of normotensive type I diabetic patients with microalbuminuria, no captopril group subjects had hyperkalemia (0/116). (See PRECAUTIONS: Drug Interactions; ADVERSE REACTIONS: Altered Laboratory Findings.) *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. *Valvular Stenosis* — A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia* — If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion. **Hemodialysis:** Recent clinical observations have shown an association of hypersensitivity-like (anaphylactoid) reactions during hemodialysis with high-flux dialysis membranes (e.g., AN69) in patients receiving ACE inhibitors. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of medication. **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. **Drug Interactions:** *Hypotension — Patients on Diuretic Therapy* — Precipitous reduction of blood pressure may occasionally occur within the first hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. The possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about one week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least one hour after the initial dose. *Agents Having Vasodilator Activity* — In heart failure patients, vasodilators should be administered with caution. *Agents Causing Renin Release:* Captopril's effect will be augmented by antihypertensive agents that cause renin release. *Agents Affecting Sympathetic Activity* — The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution. *Agents Increasing Serum Potassium* — Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution. *Inhibitors Of Endogenous Prostaglandin Synthesis* — Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension. *Lithium* — Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity. **Drug/Laboratory Test Interaction:** Captopril may cause a false-positive urine test for acetone. **Carcinogenesis, Mutagenesis and Impairment of Fertility:** Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential.The high dose in these studies is 150 times the maximum recommended human dose of 450 mg, assuming a 50-kg subject. On a body-surface-area basis, the high doses for mice and rats are 13 and 26 times the maximum recommended human dose, respectively. Studies in rats have revealed no impairment of fertility.

Pregnancy Categories C (first trimester) and D (second and third trimesters).
See WARNINGS: Fetal/Neonatal Morbidity and Mortality.
Nursing Mothers: Concentrations of captopril in human milk are approximately one percent of those in maternal blood. Because of the potential for serious adverse reactions in nursing infants from captopril, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of CAPOTEN (captopril) to the mother. (See PRECAUTIONS: Pediatric Use.) **Pediatric Use:** Safety and effectiveness in children have not been established. There is limited experience reported in the literature with the use of captopril in the pediatric population; dosage, on a weight basis, was generally reported to be comparable to or less than that used in adults. Infants, especially newborns, may be more susceptible to the adverse hemodynamic effects of captopril. Excessive, prolonged and unpredictable decreases in blood pressure and associated complications, including oliguria and seizures, have been reported. CAPOTEN should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients. *Renal:* About one of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients. *Hematologic:* Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported. *Dermatologic:* Rash, (usually maculopapular, rarely urticarial) often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the first four weeks of therapy. Pruritus, without rash, occurs in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Flushing or pallor has been reported in 2 to 5 of 1000 patients. *Cardiovascular:* Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension with captopril therapy. Tachycardia, chest pain, and palpitations have each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure in 2 to 3 of 1000 patients. *Dysgeusia:* Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). *Angioedema:* Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See WARNINGS.) *Cough:* Cough has been reported in 0.5-2% of patients treated with captopril in clinical trials. (See PRECAUTIONS: General, Cough). The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, alopecia, paresthesias. Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined. *Body as a whole:* Anaphylactoid reactions (see PRECAUTIONS: Hemodialysis). *General:* Asthenia, gynecomastia. *Cardiovascular:* Cardiac arrest, cerebrovascular accident/insufficiency, rhythm disturbances, orthostatic hypotension, syncope. *Dermatologic:* Bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis. *Gastrointestinal:* Pancreatitis, glossitis, dyspepsia. *Hematologic:* Anemia, including aplastic and hemolytic. *Hepatobiliary:* Jaundice, hepatitis, including rare cases of necrosis, cholestasis. *Metabolic:* Symptomatic hyponatremia. *Musculoskeletal:* Myalgia, myasthenia. *Nervous/Psychiatric:* Ataxia, confusion, depression, nervousness, somnolence. *Respiratory:* Bronchospasm, eosinophilic pneumonitis, rhinitis. *Special Senses:* Blurred vision. *Urogenital:* Impotence. As with other ACE inhibitors, a syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR. **Fetal/Neonatal Morbidity and Mortality. See WARNINGS: Fetal/Neonatal Morbidity and Mortality. Altered Laboratory Findings:** *Serum Electrolytes: Hyperkalemia:* small increases in serum potassium, especially in patients with renal impairment (see PRECAUTIONS). *Hyponatremia:* particularly in patients receiving a low sodium diet or concomitant diuretics. *BUN/Serum Creatinine:* Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of longstanding or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine. *Hematologic:* A positive ANA has been reported. *Liver Function Tests:* Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

DOSAGE AND ADMINISTRATION: CAPOTEN should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension, heart failure, LVD after myocardial infarction and diabetic nephropathy. Because CAPOTEN is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function. (See also PRECAUTIONS: Hemodialysis).
[Consult package insert before prescribing CAPOTEN (captopril).]

HOW SUPPLIED: Available in tablets of 12.5 mg in bottles of 100 and 1000; 25 mg in bottles of 100 and 1000; 50 mg in bottles of 100 and 1000; 100 mg in bottles of 100; and in Unimatic® unit-dose packs containing 100 tablets.

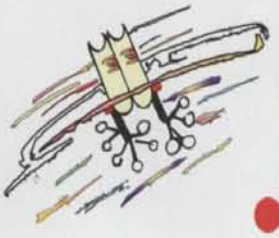
(J4-458E)

References: 1. Lewis EJ, Hunsicker LG, Bain RP, et al: The effect of angiotensin-converting–enzyme inhibition on diabetic nephropathy. *N Engl J Med* 329:1456-1462, 1993. **2.** Data on file, Bristol-Myers Squibb Pharmaceutical Research Institute.

Bristol-Myers Squibb Company

F1-K009 Issued: April 1994 Printed in USA

JOIN US IN NEW ORLEANS FOR THE 54TH ANNUAL SCIENTIFIC SESSIONS



The 54th Annual Scientific Sessions will feature four full days of major lectures, symposia, oral and poster presentations, poster discussion sessions, state-of-the-art lectures, and workshops.

Program Overview

Saturday, June 11

Professional Section Council Symposia

8:30 - 12:00 noon

- Gestational Diabetes: What Is It and What Should We Do About It?
- Post DCCT Insights into the Care of Children and Adolescents
- How to Intensify Diabetes Management in the Real World: Four Perspectives
- Clinical Issues and Strategies in Management of the Diabetic Foot
- Impact of the DCCT on Health Care Delivery and Public Health
- The DCCT - One Year Later

1:30 - 5:00 pm

- Assessment of Psychosocial Status and Self-Treatment Behavior in Diabetic Patients: The first Step Toward Effective Intervention
- Diabetes: The Role of Micronutrients
- Screening for Diabetes Mellitus in Adults
- Metabolic Control and Complications: How Much and How
- Exercise Through the Ages
- Insulin Signal Transduction

Sunday, June 12

8:15 - 10:15 am

Concurrent Symposia

- Strategies for Finding the Diabetes Genes
- The Energy Balance Equation

10:30 - 1:30 pm

- Oral Abstract Presentations
- General Poster Session

1:30 - 3:30 pm

- Oral Abstract Presentations
- State-of-the-Art Lectures
- Workshops
- Poster Discussion Sessions

3:45 - 5:00 pm

- President's Address
- Banting Lecture

5:30 - 7:30 pm

- President's Poster Session
  Advances in NIDDM

Monday, June 13

8:15 - 10:15 am

Concurrent Symposia

- Etiology of NIDDM
- Small GTP Binding Proteins: Potential Role in Insulin Action and Insulin Secretion
- Hypoglycemia: Critical Issues in Diabetes Management

10:30 - 1:30 pm

- Oral Abstract Presentations
- General Poster Session

1:30 - 3:30 pm

- Oral Abstract Presentations
- Workshops
- Poster Discussion Sessions

3:45 - 5:00 pm

- Scientific Awards Presentation
- Lilly Lecture

Tuesday, June 14

8:15 - 10:15 am

Concurrent Symposia

- Insulin Resistance and Hypertension: A Second Look
- Animal Models of Obesity and Diabetes
- Changing Behavior

10:30 - 1:30 pm

- Oral Abstract Presentations
- General Poster Session

1:30 - 3:30 pm

- Oral Abstract Presentations
- State-of-the-Art Lectures
- Workshops
- Poster Discussion Sessions

JUNE 11-14, 1994

New this year

Small Group Workshops on:

- Initiation of Intensive Insulin Therapy •
- Hypoglycemia •
- Therapeutic Choices in NIDDM •
- Treatment of Lipid Disorders in Diabetes •
- Changing Behavior •
- Creative Approaches to Effective Patient Education •

The Banting Lecture -
Philip E. Cryer, MD
Hypoglycemia:
The Limiting Factor of IDDM

The Lilly Lecture -
Kenneth S. Polonsky,MD
The Beta-Cell in Diabetes:
From Molecular Genetics to
Clinical Research

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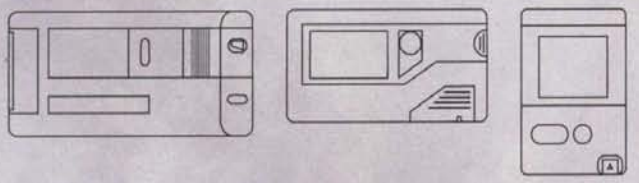

What it takes to take control

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NOTICE TO AUTHORS

The American Diabetes Association will begin charging authors $50 per printed page beginning with articles published in the September 1994 issues of *Diabetes* and *Diabetes Care*. These charges will partially defray the rising costs of publication. Although editorial consideration and acceptance of a paper is in no way related to payment of a page charge, it is expected that authors will pay the page charge. In extraordinary cases, upon appeal by the author, the Publications Policy Committee may waive the page charge.

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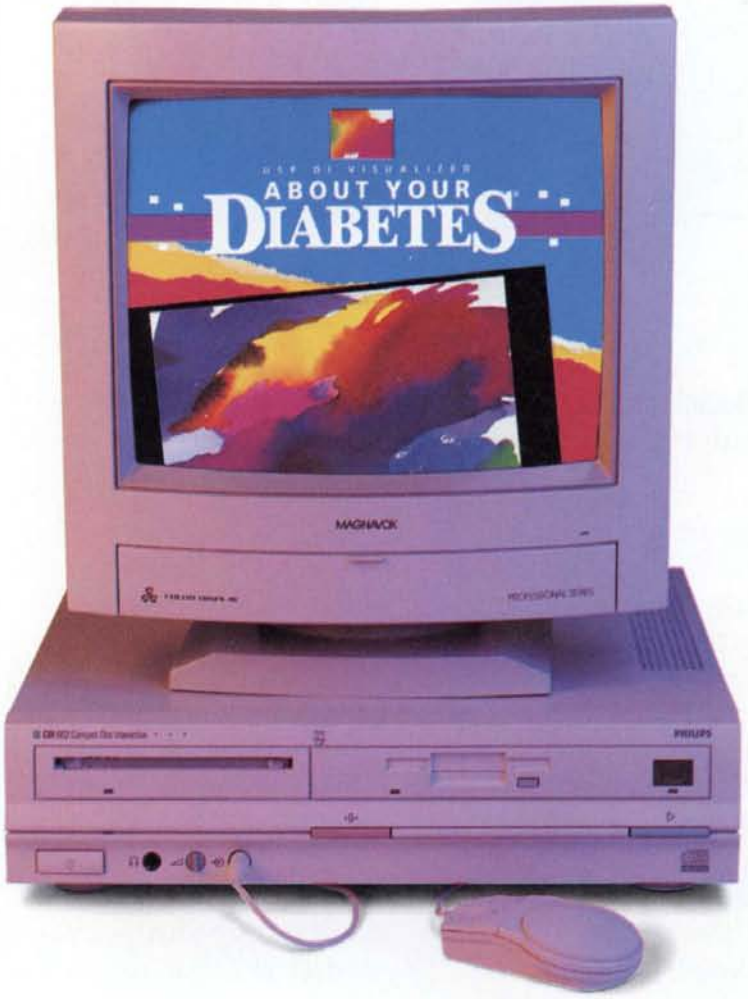

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Medical Management of Type II Diabetes

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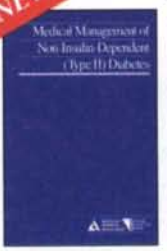

formerly: *Physician's Guide to Type II Diabetes*

Thousands have come to rely on the *Physician's Guide* for diagnosing and treating type II diabetes and now the best just got better! This long-awaited revision provides critical information for front-line health professionals and diabetes specialists alike. Completely revised and updated, it features all the latest information on managing type II diabetes—presented in one concise, well-organized guide. Softcover; #PMMT2.

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A must-read for anyone who treats women with type I, type II, or gestational diabetes! The book is comprehensive, yet concise, taking 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. Tabbed and well-indexed for easy access to important information.
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Note: Sets available in July; books sold as sets cannot be sold separately.

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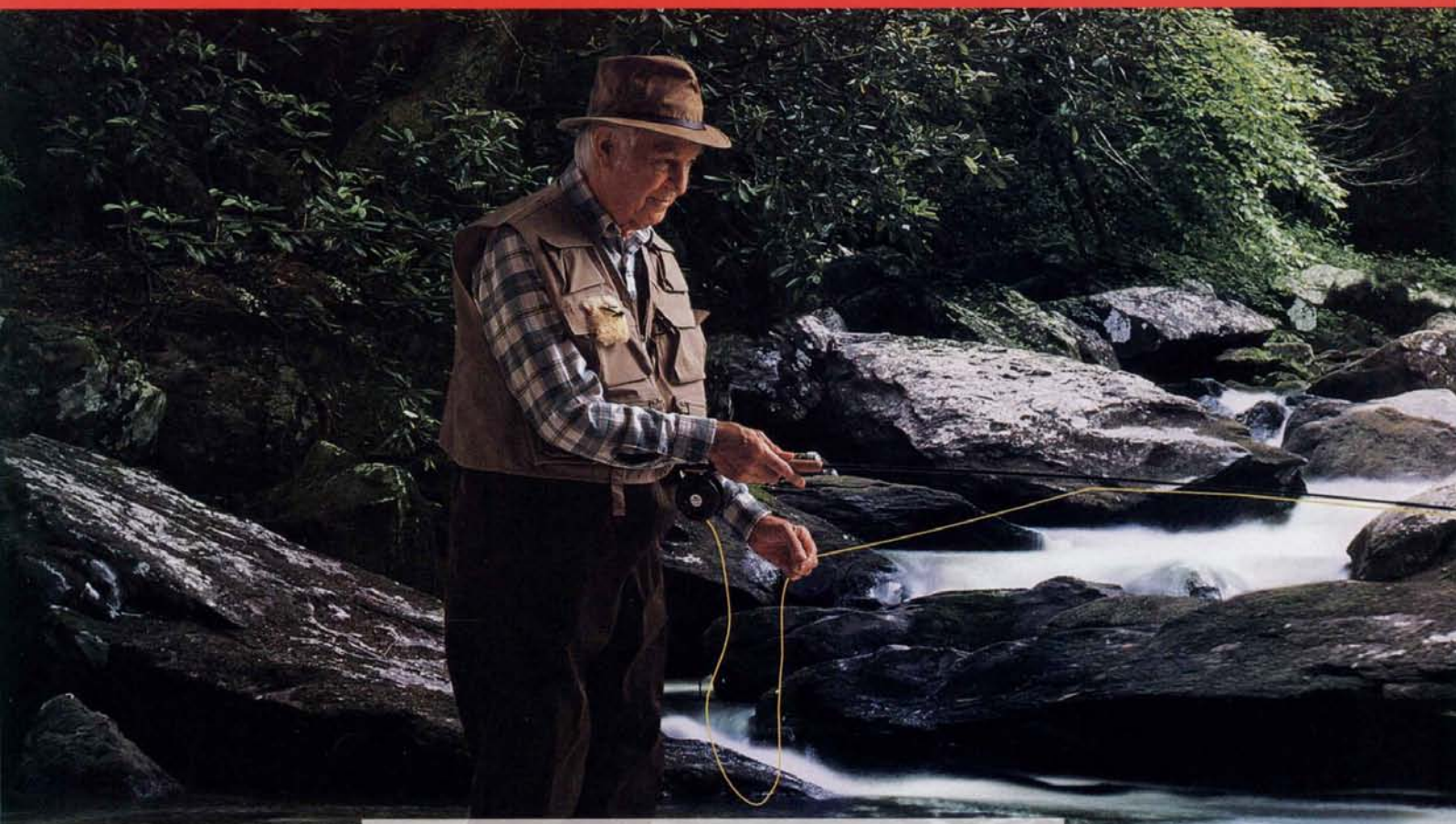

BENEFIT FROM THE EXPERIENCE

- Proven 24-hour control in hypertension
- Proven 24-hour control in angina
- Over 1.8 billion patient therapy days reported*

EXPERIENCE THE BENEFITS

- Well tolerated
- Effective in a wide range of patient types[1-5]
- Consistent 24-hour plasma levels[6]
- No clinically significant effect on heart rate[2,3]

once-a-day

PROCARDIA XL®

(nifedipine) extended release

Tablets 30mg, 60mg and 90mg GITS

*Methodology on file at Pratt Pharmaceuticals, derived from NPA Plus™, IMS America, Ltd., 1993.

Please see brief summary of prescribing information on adjacent page .

once-a-day

PROCARDIA XL®

(nifedipine) extended release

Tablets 30mg, 60mg and 90mg GITS

TRUST THE EXPERIENCE

CONVENIENT DOSING

- Easy to titrate
- Convenient AM or PM dosing
- Can be taken with or without food

WELL-TOLERATED THERAPY

Side effects include peripheral edema, which is not associated with fluid retention, and headache

In controlled clinical trials of 776 patients with PROCARDIA XL, edema resulted in discontinuation of therapy in 2.6% of patients[6]

References: **1.** Monsen L, Moisey D, Gaffney M, Fischer J, the Nifedipine GITS Study Group. Consistent blood pressure reduction without loss of diurnal variability with once-daily nifedipine GITS treatment. *Am J Hypertens.* 1990;3(2):114A. Abstract. **2.** Parmley WW, Nesto RW, Singh BN, Deanfield J, Gottlieb SO, the N-CAP Study Group. Attenuation of the circadian patterns of myocardial ischemia with nifedipine GITS in patients with chronic stable angina. *J Am Coll Cardiol.* 1992;19:1380-1389. **3.** Phillips RA, Ardeljan M, Shimabukuro S, et al. Effects of nifedipine-GITS on left ventricular mass and left ventricular filling. *J Cardiovasc Pharmacol.* 1992;19 (suppl 2):S28-S34. **4.** Sheu WH-H, Swislocki ALM, Hoffman B, Chen Y-DI, Reaven GM. Comparison of the effects of atenolol and nifedipine on glucose, insulin, and lipid metabolism in patients with hypertension. *Am J Hypertens.* 1991;4:199-205. **5.** Reams G, Lau A, Knaus V, Bauer JH. The effect of nifedipine GITS on renal function in hypertensive patients with renal insufficiency. *J Clin Pharmacol.* 1991;31:468-472. **6.** Data on file. Pfizer Inc, New York, NY.

Brief Summary
PROCARDIA XL® (nifedipine) Extended Release Tablets For Oral Use

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, gastro-esophageal 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. Revised October 1992

HD098B94

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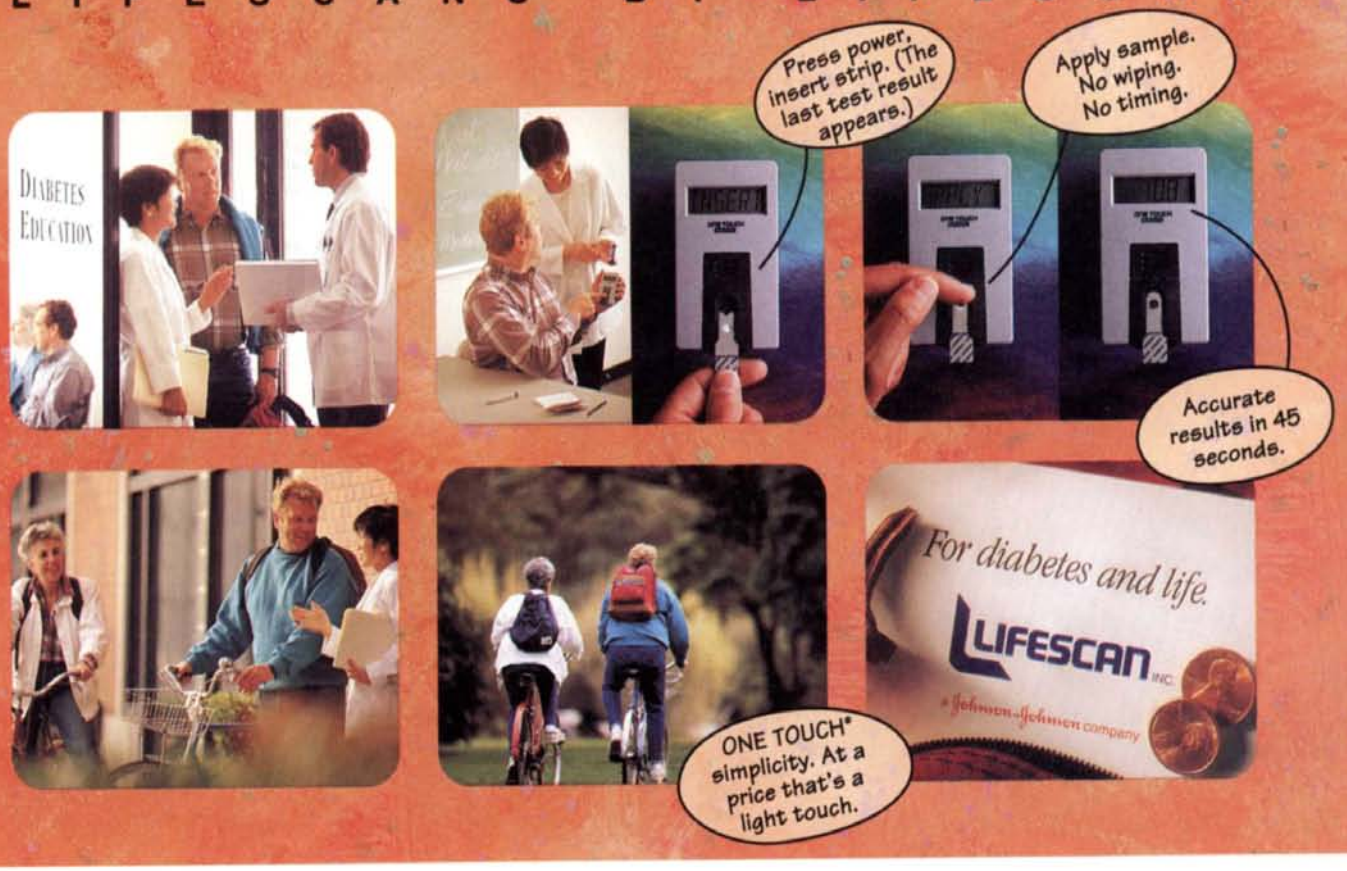

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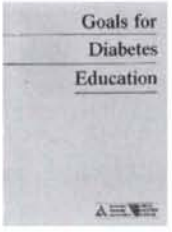

Education is key in managing diabetes and this book provides you with a logical, thorough approach to the initial and in-depth phases of educating patients. Covers specific goals for each content area in a convenient checklist format.
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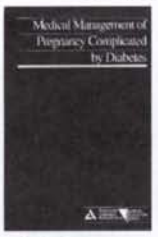

Comprehensive, yet concise! Takes you through every aspect of pregnancy and diabetes from prepregnancy counseling to postpartum follow-up and everything in between. Provides precise protocols for treatment of both pre-existing and gestational diabetes. A must-read! Softcover; 136 pp. #PMMPCD
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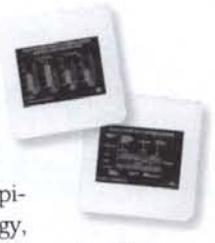

This 3-hour program focuses on diabetes and its complications as risk factors for atherosclerotic vascular disease. Covers epidemiology, pathophysiology, assessment, and treatment for each risk factor. Includes case study discussion and presenter's script. 97 slides. #PMCEP3SS
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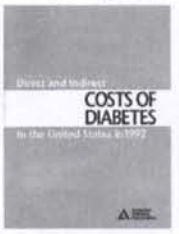

Takes a hard look at the economic impact of diabetes on our nation. If $90 billion seems like a lot to you, then you need to get this book. That's how much diabetes cost this country in medical expenses and lost productivity from premature death and disability in a single year. Softcover; 32 pp.; #PMDIC92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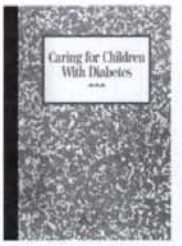

Teachers, school nurses, day-care providers, camp personnel—they all have responsibility for children, so when a child has diabetes, they need to know what's involved. This book will help them understand the disease and how to recognize and react to a diabetes emergency. Softcover; 16 pp. #PECARCH
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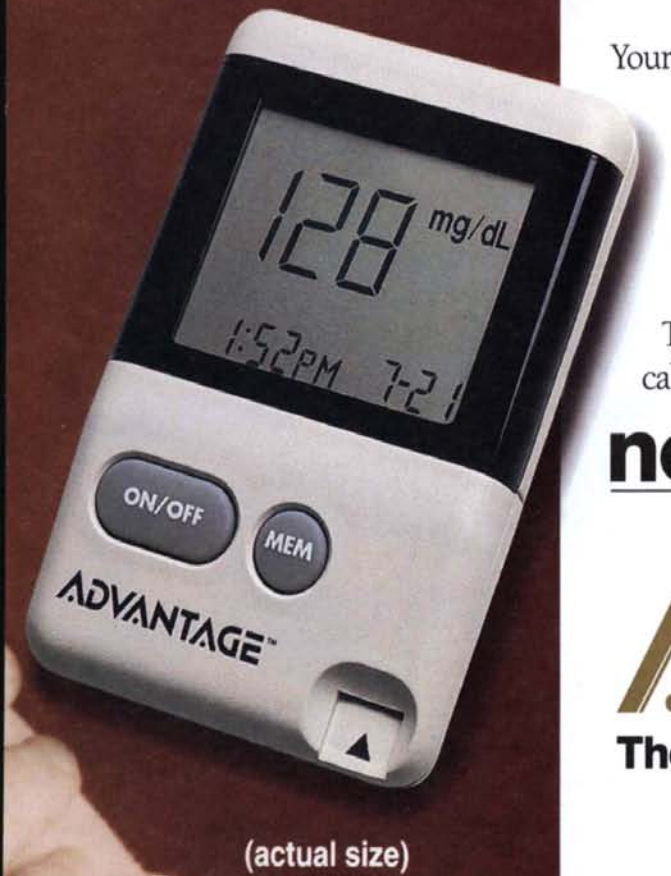

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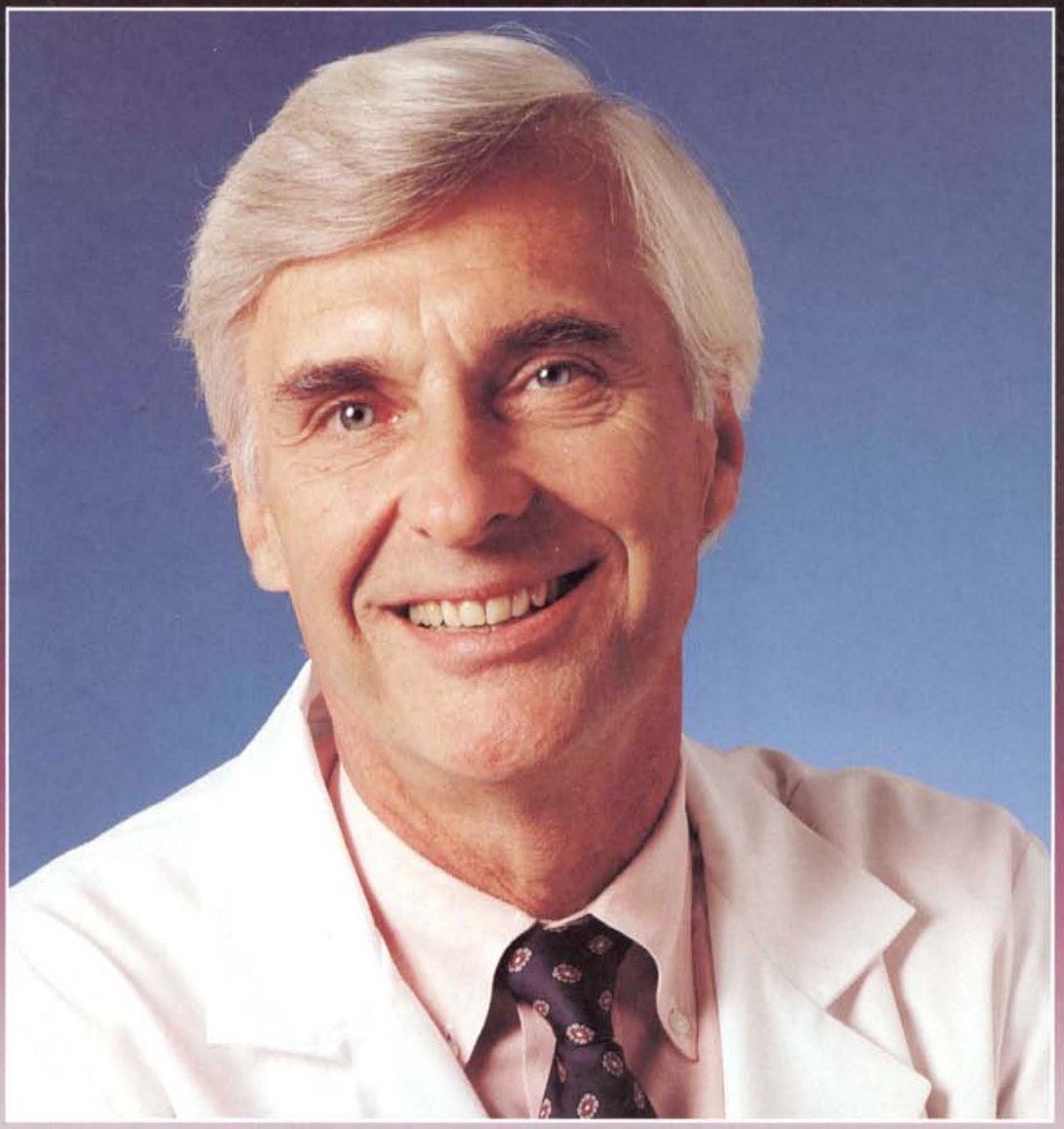

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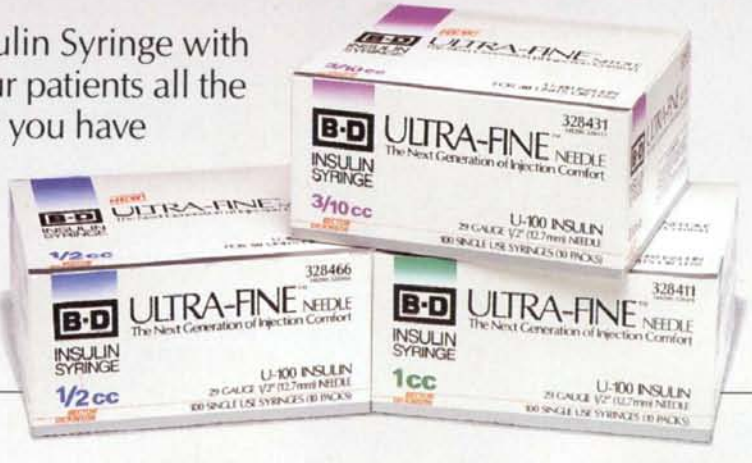

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