THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

Diabetes Care

VOLUME 15 NUMBER 9

Review Issue

SEPTEMBER 1992

American Diabetes Association.

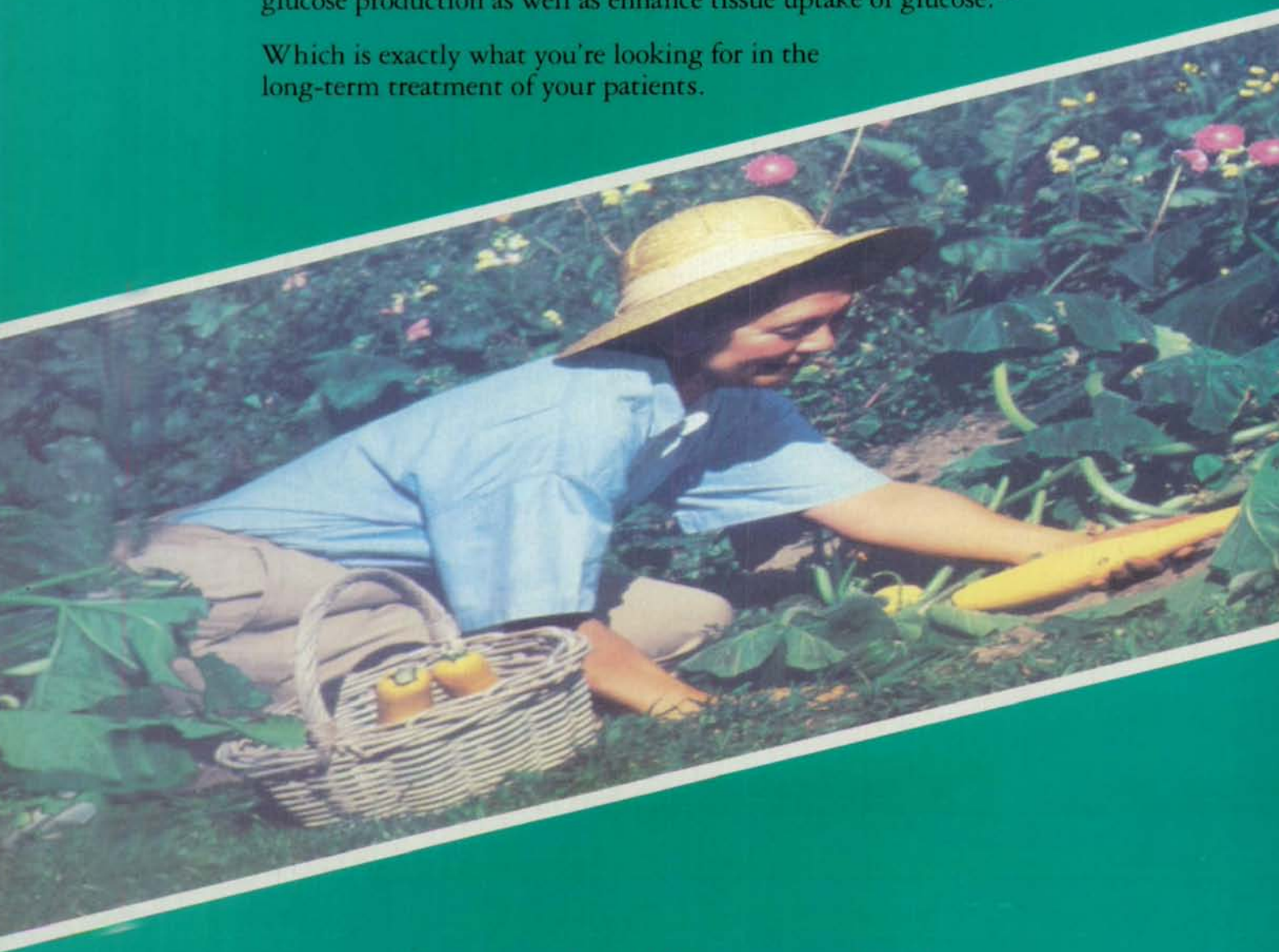
ISSN 0149-5992

Because type II diabetes therapy *stretches* from months into years...

Therapy for type II diabetic patients is almost always long term. So it's reassuring to know that DiaBeta® (glyburide) has been shown to provide important long-term benefit.

With chronic administration of DiaBeta®, there is evidence to suggest that excellent long-term glycemic control can be achieved, and achieved without sustained high levels of insulin. In fact, glyburide appears to reduce hepatic glucose production as well as enhance tissue uptake of glucose.[1-4]

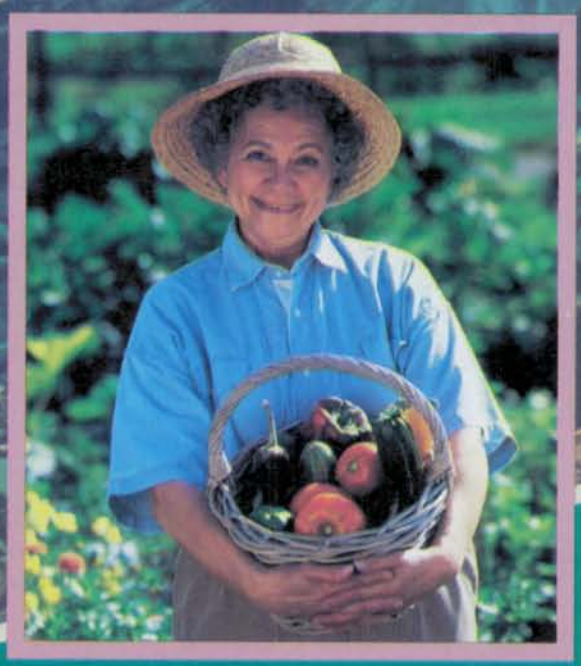
Which is exactly what you're looking for in the long-term treatment of your patients.



All sulfonylureas, including DiaBeta®, can cause severe hypoglycemia.

Choose DiaBeta®.

GLYCEMIC CONTROL FOR THE LONG TERM



DiaBeta® TABLETS 1.25, 2.5 & 5 mg

GLYBURIDE / HOECHST-ROUSSEL

Long-term therapy for a long-term disease

Please see next page for brief summary of prescribing information.

Duality of Interest Policy

The American Diabetes Association recently approved a new duality of interest policy covering authors in Association publications.

Starting immediately, authors of manuscripts accepted for publication will now receive a duality of interest disclosure form. All authors must complete and return the statement prior to publication of the manuscript. If an author indicates that a possible duality of interest exists, the Association may disclose its existence, but not its nature. The decision to disclose a duality of interest will be made by the editorial office. The disclosure will take the form of an asterisk by the author's name in the publication. The asterisk will refer to a statement elsewhere in the publication indicating that such an author has indicated that a potential duality of interest may exist. As an alternative, the Association will allow the author to disclose exactly the nature of the dual interest, which will appear as a footnote in the author's article.

Authors may decline to complete this form. In that event, the Association will not publish their manuscript. Such a decision will in no way bias publication of future manuscripts on the same or other subjects.

The American Diabetes Association considers that there may be a duality of interest when an author has a relationship with an industrial concern whose products or services are *directly* related to the subject matter of the manuscript. Such relationships include: employment by an industrial concern, ownership of stock, membership on a committee or the board of directors, receipt of honoraria or consulting fees, or receipt of grants or funds from such corporations or individuals representing such corporations.

Authors submitting articles for publication should consider the subject matter they are presenting in light of any relationship as delineated above. If the author believes that a real or perceived conflict may arise by virtue of the content of his or her manuscript, then the author should disclose the nature of the dual interests on the duality of interest statement or reconsider submitting the manuscript to the American Diabetes Association.

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

VOLUME 15 NUMBER 9

Diabetes Care

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

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

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

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

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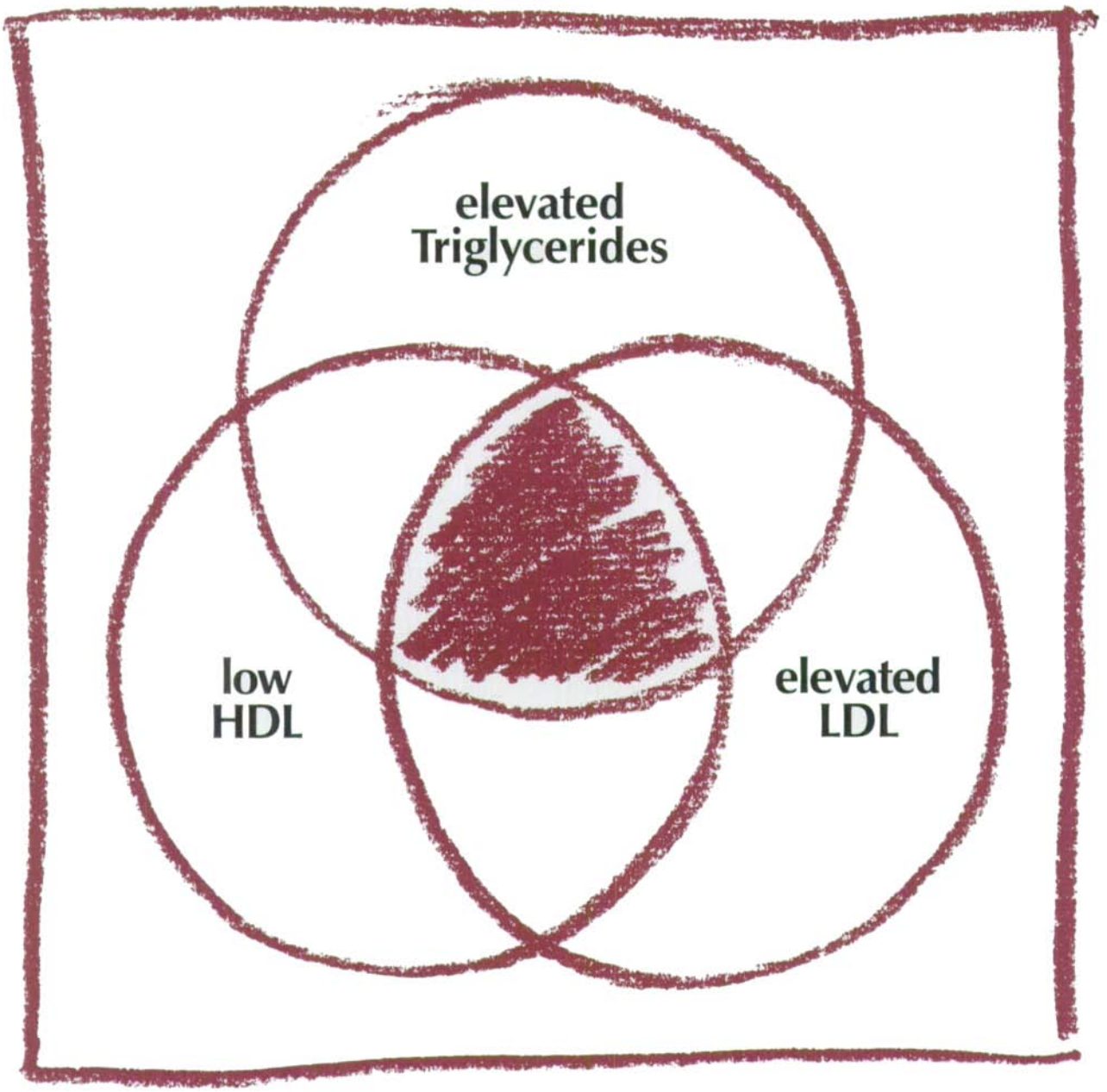
Reduce the risk of developing CHD in patients with the triad of risk...



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

LOPID®

(gemfibrozil) 600-mg Tablets BID

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

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

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

and

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

In addition:

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

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

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

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

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

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BOOTS PHARMACEUTICALS

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

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

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

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary heart disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. IN VIRTUALLY ALL PATIENTS WHO HAVE HAD AN UNSATISFACTORY LIPID RESPONSE TO EITHER DRUG ALONE, ANY POTENTIAL LIPID BENEFIT OF COMBINED THERAPY WITH LOVASTATIN AND GEMFIBROZIL DOES NOT OUTWEIGH THE RISKS OF SEVERE MYOPATHY, RHABDOMYOLYSIS, AND ACUTE RENAL FAILURE (see Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS

1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **HMG-CoA reductase inhibitors:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin (or other HMG-CoA reductase inhibitors) and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

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

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

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

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

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

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

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

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

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

6. **Nursing Mothers** – It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for Lopid in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in *occasional patients following initiation of Lopid therapy.* However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Kidney Function** – There have been reports of worsening renal insufficiency upon the addition of Lopid therapy in individuals with baseline plasma creatinine > 2.0 mg/dL. In such patients, the use of alternative therapy should be considered against the risks and benefits of a lower dose of Lopid.

10. **Use in Children** – Safety and efficacy in children and adolescents have not been established.

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

DOSAGE AND ADMINISTRATION

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

OVERDOSAGE

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

HOW SUPPLIED

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

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

Storage: Store below 30° C (86° F).

REFERENCES

1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245.
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4. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol. *Arch Int Med* 1988;148:36-39.

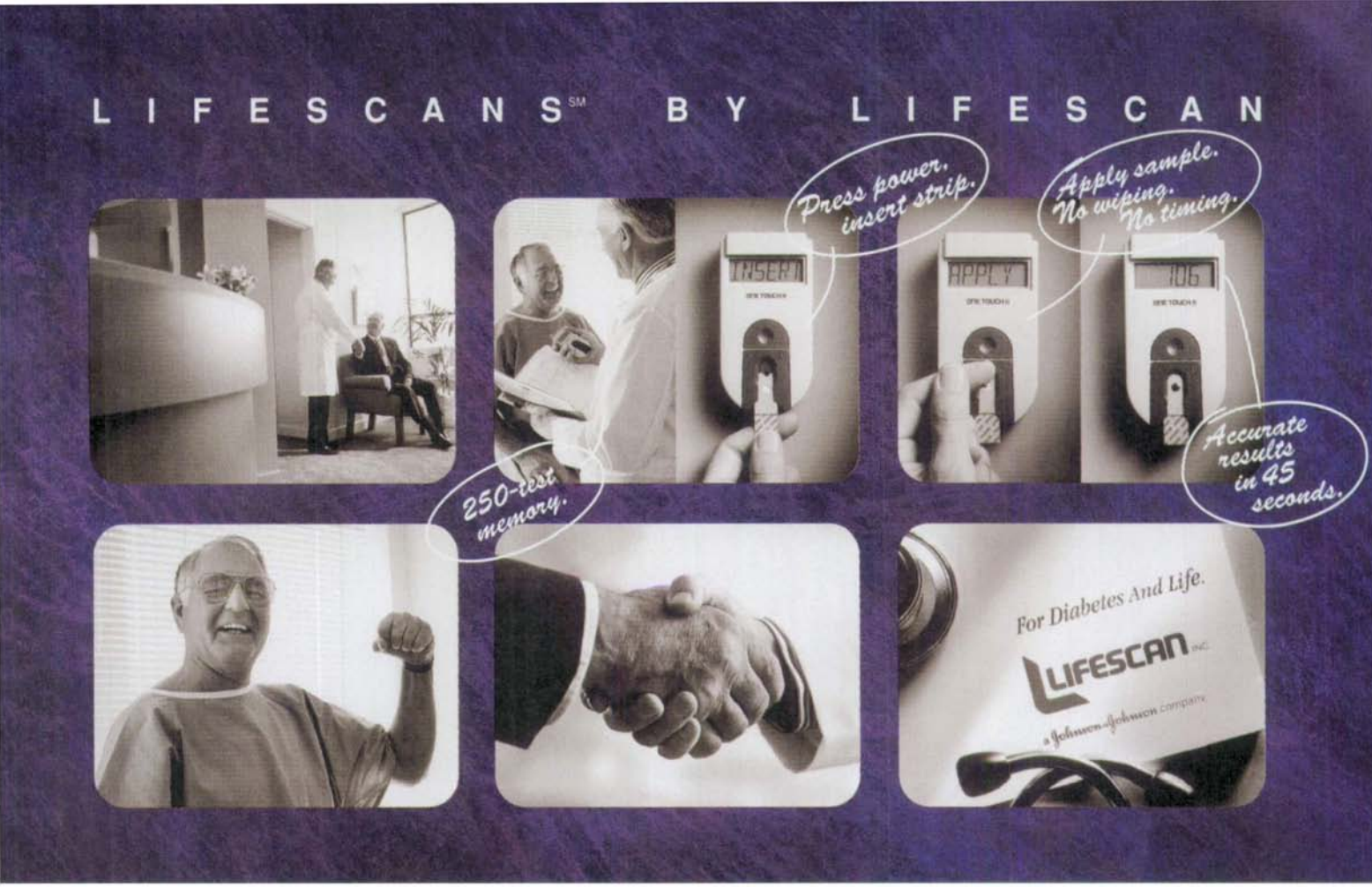
Caution – Federal law prohibits dispensing without prescription.

0737G015

Revised April 1992

PARKE-DAVIS
Division of Warner-Lambert Company
Morris Plains, NJ 07950 USA

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



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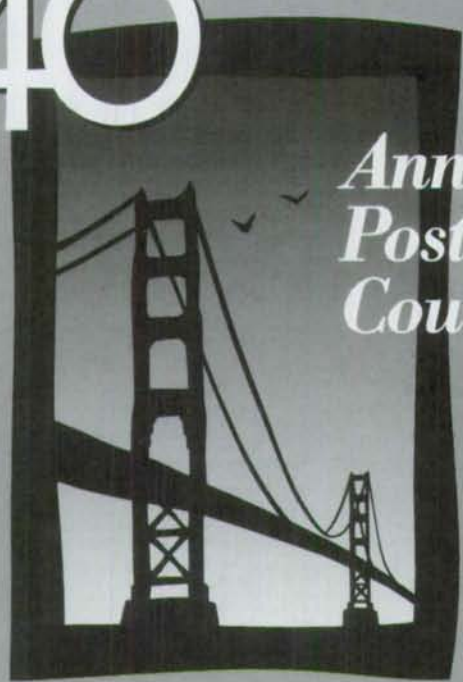

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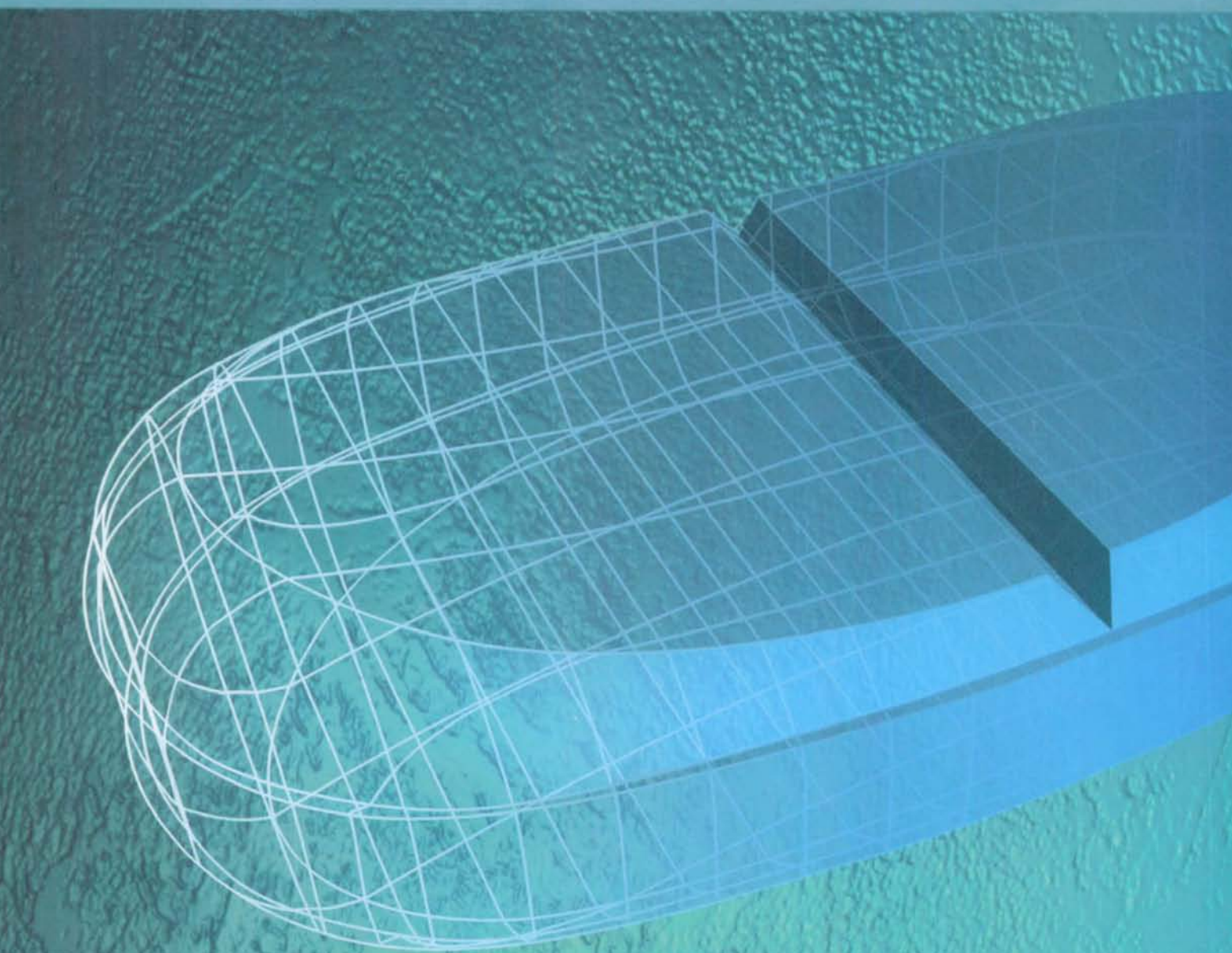

INTRODUCING

GLYNASE™ PRESTAB™

Tablets (glyburide) **3mg**

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GLYNASE PresTab: Designed for greater flexibility

A patented manufacturing process has created a unique tablet* that divides easily and evenly in half at the press of a finger. This breakthrough in dosing flexibility enables ease of titration for the individual dosing needs of your patients.

*Upjohn Utility Patent #4735805.

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R_x 3 mg

GLYNASE PresTab: Designed for control at a lower dose

GLYNASE PresTab 3 mg is a new formulation of glyburide, providing improved, more consistent bioavailability due to enhanced absorption.[1] Now it is possible to provide effective blood glucose control with a lower dose.

GLYNASE PresTab: Designed to deliver

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

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

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

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GLYNASE™ PRESTAB™

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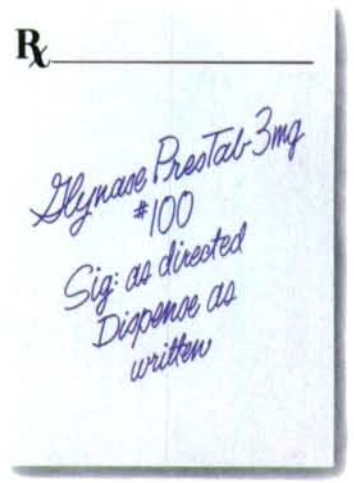
- The 3-mg tablet breaks easily and evenly to titrate in 1.5-mg increments, providing eight different doses ranging from 1.5 mg to 12 mg.
- The 1.5-mg tablet may be easily broken to provide the infrequent .75-mg dose.
- Patients should be retitrated when transferred from Micronase® (glyburide) or other oral hypoglycemic agents.



Start with one-half or one 3-mg GLYNASE PresTab daily.

3 mg 1.5 mg

	GLYNASE PresTab	Micronase	Glucotrol*	Diabinese†
Usual Starting Dose	1.5 mg to 3 mg	2.5 mg to 5 mg	5 mg	250 mg
Daily Dosage Range	.75 mg to 12 mg	1.25 mg to 20 mg	2.5 mg to 40 mg	100 mg to 750 mg

*Glucotrol (glipizide) is a trademark of Roerig.

†Diabinese (chlorpropamide) is a trademark of Pfizer Laboratories.

GLYNASE™ PresTab™ Tablets
(glyburide)

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

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

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 g per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of GLYNASE PresTab and of alternative modes of therapy.

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

PRECAUTIONS

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

General

Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection and dosage and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may increase the risk of serious hypoglycemic reactions. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking ß-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used. **Loss of Control of Blood Glucose:** In stabilized diabetic patients exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue GLYNASE PresTab and administer insulin. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as secondary failure. **Information for Patients**: Patients should be informed of the potential risks and advantages of GLYNASE PresTab and of alternative modes of therapy. They also should be informed about the impbrtance of adherence to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Laboratory Tests

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

Drug Interactions

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and ß-adrenergic blocking agents.

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

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. It is not known whether this reaction also occurs with intravenous, topical, or vaginal miconazole.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Pregnancy

Teratogenic Effects: Pregnancy Category B

Reproduction studies in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus due to glyburide. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Many experts recommend that insulin be used during pregnancy to maintain blood glucose as close to normal as possible. Nonteratogenic Effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently for agents with prolonged half-lives. If used during pregnancy, GLYNASE PresTab should be discontinued at least 2 weeks before the expected delivery date.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Hypoglycemia: See Precautions and Overdosage sections. **Gastrointestinal Reactions:** Cholestatic jaundice and hepatitis may occur rarely; GLYNASE PresTab Tablets should be discontinued if this occurs. Liver function abnormalities have been reported. Gastrointestinal disturbances (eg, nausea, epigastric fullness, and heartburn) are the most common reactions and occurred in 1.8% of patients during clinical trials. They tend to be dose related and may disappear when the dose is reduced. **Dermatologic Reactions:** Allergic skin reactions (eg, pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions) occurred in 1.5% of patients during trials. These may be transient and may disappear despite continued use of glyburide; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas. **Hematologic Reactions:** Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas. **Metabolic Reactions**: Hepatic porphyria and disulfiramlike reactions have been reported with sulfonylureas; however, hepatic porphyria has not been reported with glyburide, and disulfiramlike reactions have been reported very rarely. Cases of hyponatremia have been reported with glyburide and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone (ADH). The syndrome of inappropriate ADH (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH or increase release of ADH, or both. **Other Reactions:** Changes in accommodation or blurred vision, or both, have been reported with glyburide and other sulfonylureas. In addition to dermatologic reactions, allergic reactions such as angioedema, arthralgia, myalgia, and vasculitis have been reported.

OVERDOSAGE

Overdosage of sulfonylureas, including glyburide, can produce hypoglycemia. Mild hypoglycemic symptoms should be treated aggressively with oral glucose and adjustments in drug dosage or meal patterns, or both. Close monitoring should continue until the physician is assured that patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurologic impairment occur infrequently but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.

HOW SUPPLIED

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

Caution: Federal law prohibits dispensing without a prescription.

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

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

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

Reference

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

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

For hypertension

ONCE-DAILY

ZESTRIL®!

LISINOPRIL · STUART

Proven power over 24 hours*

- The free *Wellspring* Service helps patients follow your healthy advice

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

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

*The antihypertensive effect may diminish at the end of the dosing interval.

Federal law prohibits participation of Medicaid patients in the Wellspring Service.

Please see adjacent page for brief summary of prescribing information.

ZESTRIL®/ LISINOPRIL-STUART

Available in 5 mg (scored), 10 mg, 20 mg, 40 mg, tablets

BRIEF SUMMARY

USE IN PREGNANCY

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

FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

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

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

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

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

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

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

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

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

PRECAUTIONS

General

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

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

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

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

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

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

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

Information for Patients

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

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

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

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

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

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

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

Drug Interactions

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

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

*Based on patient weight of 50 kg.

Zestril® (lisinopril)

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

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

Pregnancy

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

METABOLISM: Gout

MUSCULOSKELETAL: Joint pain, shoulder pain.

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

RESPIRATORY SYSTEM: Bronchitis, sinusitis, pharyngeal pain.

SKIN: Urticaria, pruritus, diaphoresis.

SPECIAL SENSES: Blurred vision.

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

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

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

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

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

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

Cough: See PRECAUTIONS - Cough

Clinical Laboratory Test Findings

Serum Electrolytes: Hyperkalemia. (See PRECAUTIONS.)

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

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

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

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

OVERDOSAGE

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

Lisinopril can be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

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

HOW SUPPLIED

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

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

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

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

Store at room temperature. Protect from moisture, freezing, and excessive heat. Dispense in a tight container.

Rev 8 02/92

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GRP 1017

MediSense Sensors. The Benefits Are Obvious. The Choice Is Simple.

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When we first introduced our exclusive BioSensor technology, the Pen™ and Companion™ sensors quickly became the fastest testing—and one of the fastest growing—blood glucose monitors available.

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Patients simply insert our patented Sensor Electrode into the sensor, apply a small drop of blood to the target area, and see accurate results in record time—now just 20 seconds.

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

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

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

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

- The two smallest monitors available: the ingeniously designed Pen 2 and the credit-card sized Companion 2.
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No monitors are as discreet or test faster than MediSense Pen 2 and Companion 2 Sensors.

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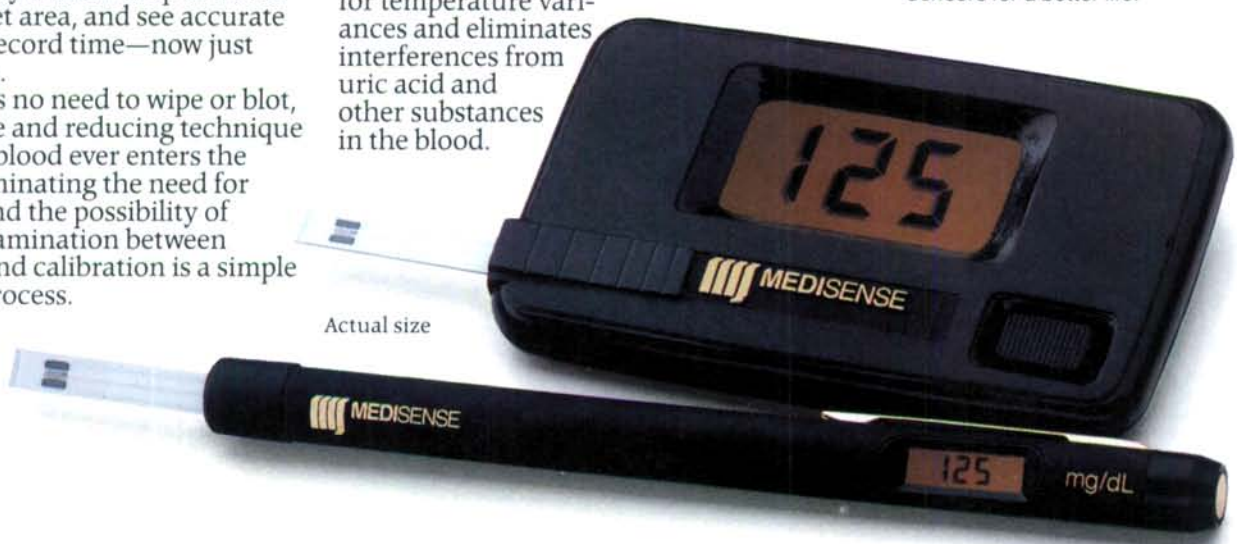
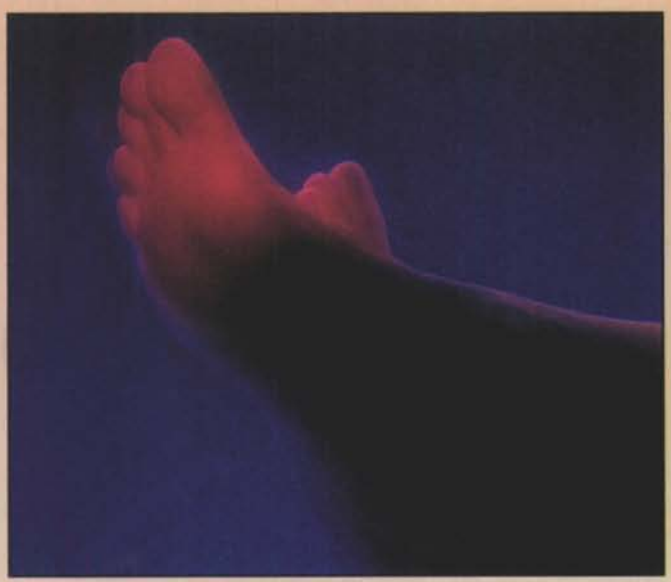
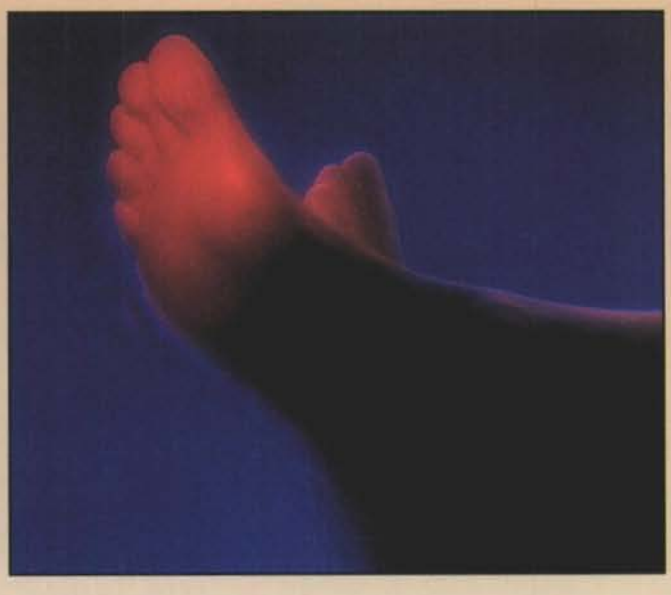


Actual size

Cambridge, MA 02139

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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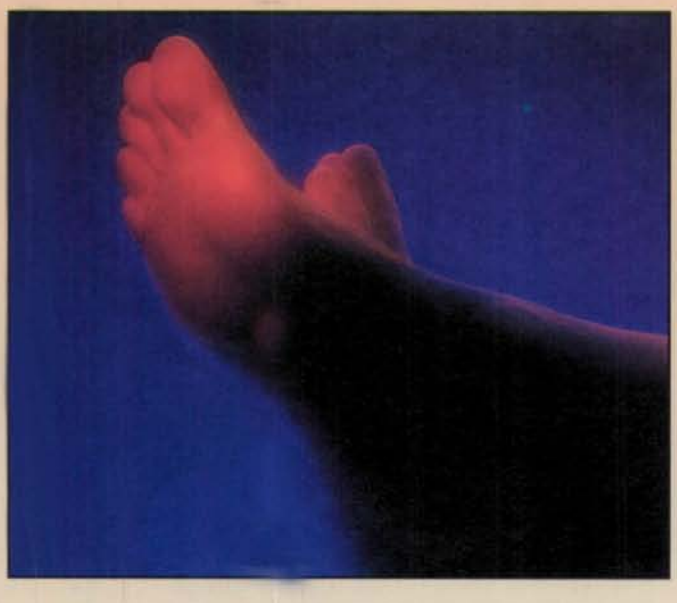

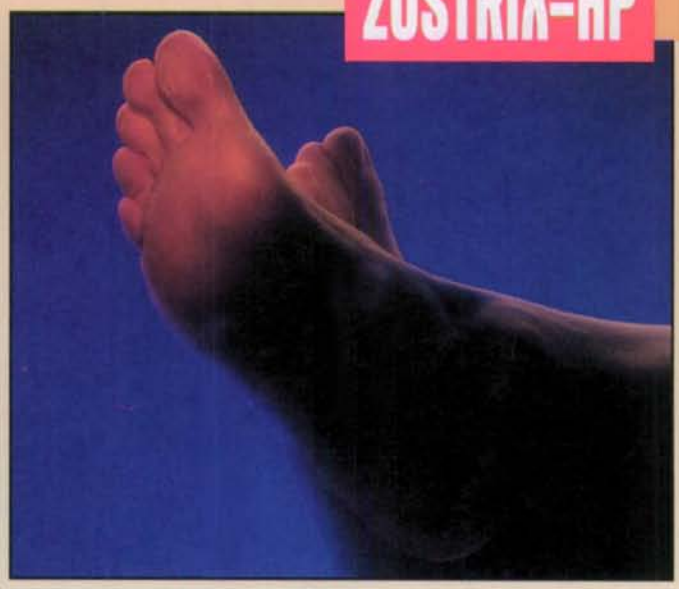

• without systemic side effects[1,2,3,4]

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

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.
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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.

Zostrix®-HP

(Capsaicin 0.075%)
Topical Analgesic Cream

Printed in U.S.A.

Z 6021 DRM-225D

ENDOCRINOLOGY, DIABETES, AND METABOLISM

On 26 September 1991, the American Board of Medical Specialties approved the request of the American Board of Internal Medicine to change the name of its Subspecialty Board on Endocrinology and Metabolism to the Subspecialty Board on Endocrinology and Metabolism. The rationale for the change is twofold: 1) to recognize the increasing complexity involved in the care of patients with diabetes and its complications and 2) to recognize that the care of patients is integral to the training and expertise of the endocrinologist.

In the time since certification in endocrinology and metabolism was introduced by the Board in 1972, major advances have occurred in the management of diabetes. The "special requirements" of the Accreditation Council for Graduate Medical Education specify that the training curriculum in endocrinology and metabolism must provide opportunities for the trainee to develop broad clinical competence in the management of patients with diabetes mellitus, including management of acute and chronic complications. The Board has kept pace with these developments in its certification process. Approximately 25% of the current certifying examination is devoted to questions on diabetes and its complications. The change in the name of the Subspecialty Board provides tangible recognition of the importance of diabetes care to the subspecialty.

Beginning with the 1991 certifying examination, all successful candidates for certification and recertification in the subspecialty will receive certificates bearing this new name. For practical reasons, the Board will not provide new certificates to its 2760 diplomates already certified in endocrinology and metabolism. However, it is understood that certification in endocrinology and metabolism before 1991 also confers recognition of special expertise in diabetes mellitus.

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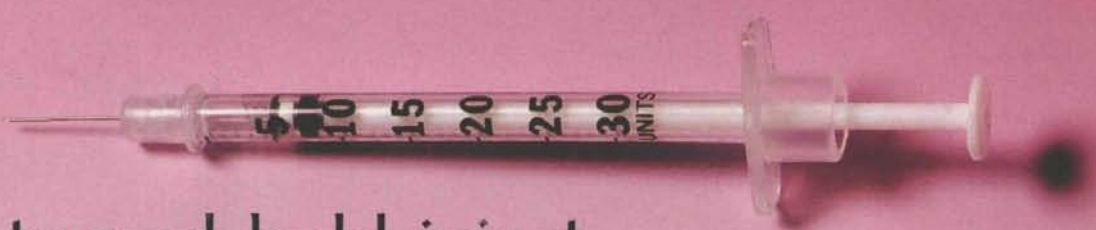

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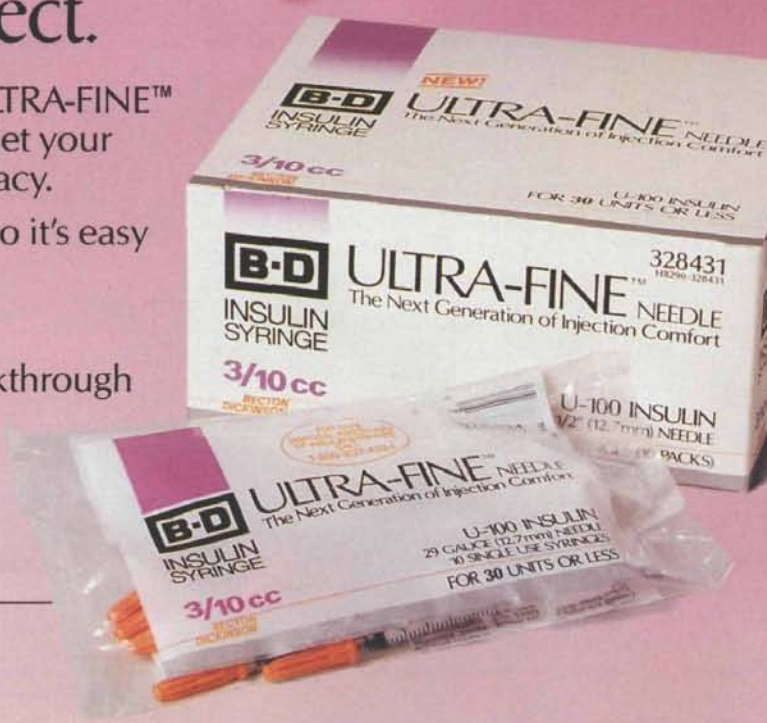
2. The single unit markings are extra wide so it's easy to read.

3. It is smaller, easier to handle.

4. The ultra-comfortable needle is the breakthrough B-D ULTRA-FINE™. . . the best there is.



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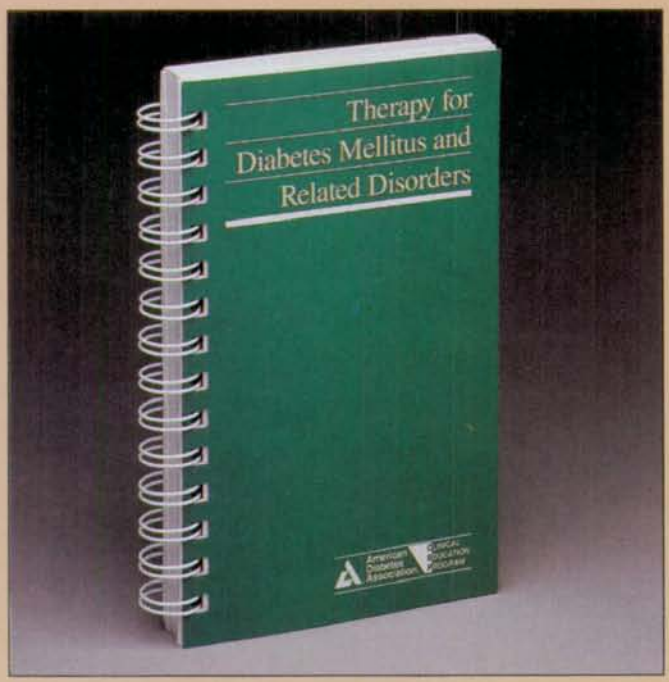

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Fact: GLUCOFILM Test Strips provide the widest hematocrit range available for blood glucose levels from 20-500 mg/dL.

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Fact: GLUCOMETER 3 Diabetes Care System is affordable.

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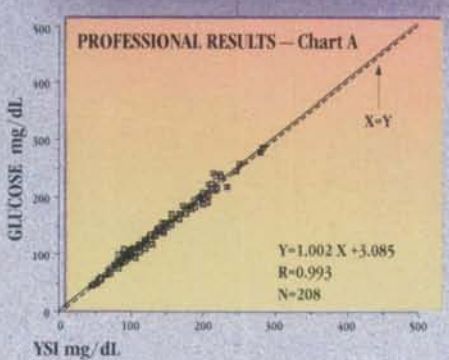

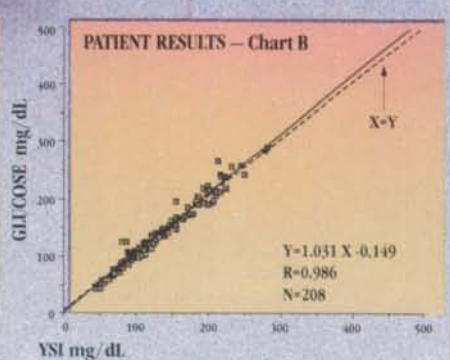

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