VOLUME 8/NUMBER 2/PAGES 107–206 MARCH/APRIL 1985

DIABETES CARE®

A PUBLICATION OF THE AMERICAN DIABETES ASSOCIATION®, INC.

ISSN 0149-5992

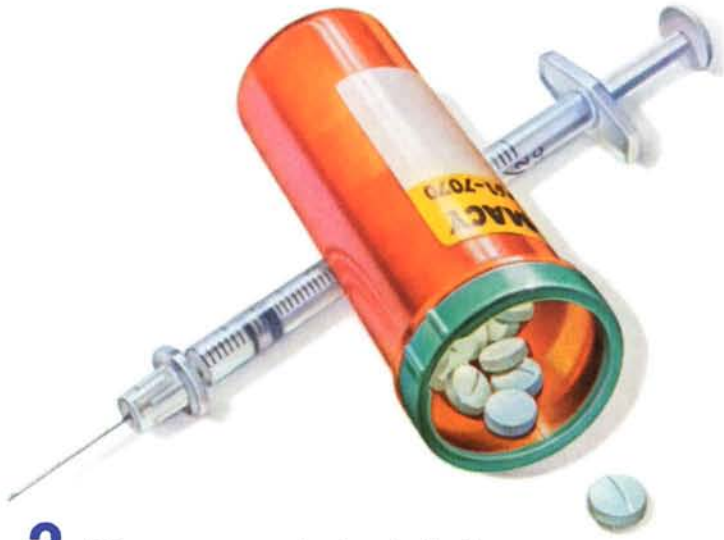
When a type II diabetic patient needs more than diet, unique MICRONASE® Tablets (glyburide) are a logical first choice.

Choosing antidiabetic

1. Micronase—a rational choice in type II diabetes

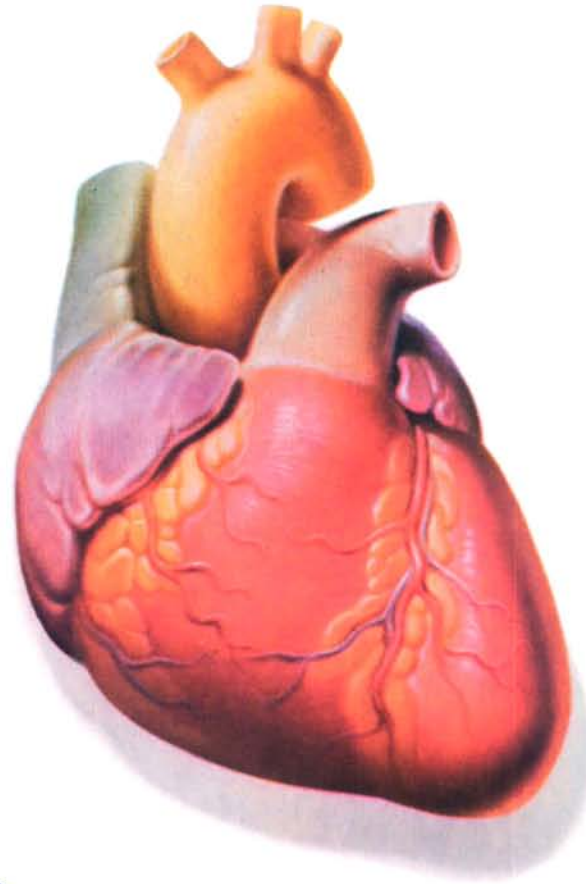
Insulin levels are normal or elevated in most patients with type II diabetes, although insulin action is markedly impaired. MICRONASE helps normalize the tissue response to endogenous insulin.

Initially, MICRONASE helps lower serum glucose in responsive patients by stimulating the release of additional insulin. As therapy continues, MICRONASE is believed to promote peripheral glucose metabolism by helping to correct defects at the cellular receptor and postreceptor levels.



2. Micronase—a single, daily dose provides 24-hour glycemic control

MICRONASE provides 24-hour control of blood glucose with a single, daily, low-milligram dose. MICRONASE may be taken with food, since food intake does not appear to affect its bioavailability.



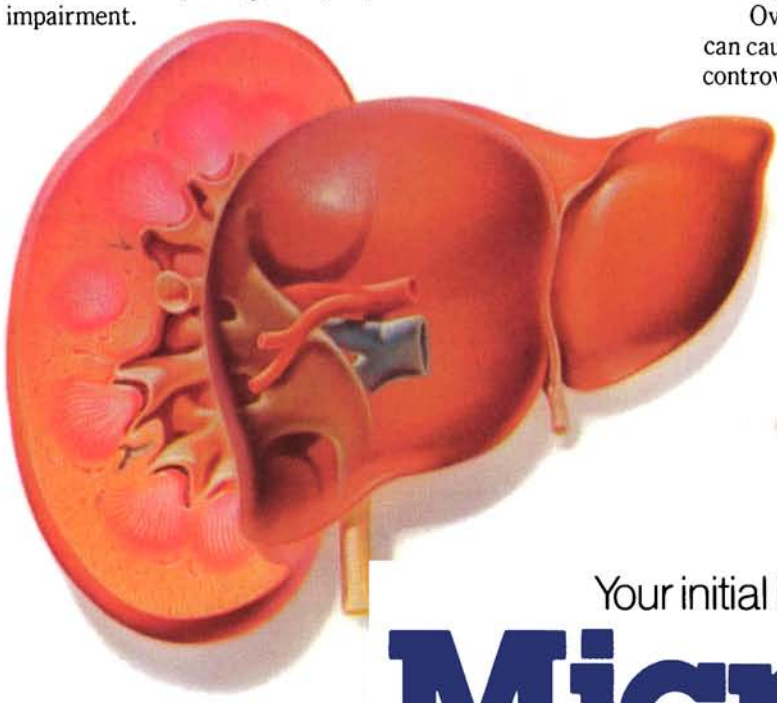
3. Micronase—for the type II diabetic patient who is also hypertensive: Control without risk of water retention

This may also be significant for the type II diabetic patient with congestive heart failure. MICRONASE actually causes a mild diuresis.

therapy today

4. Micronase—an important consideration in the type II diabetic patient with renal impairment: Control plus unique dual excretion... 50% urine, 50% bile

Elimination of MICRONASE equally in bile and urine reduces the risk of drug accumulation, which may result in hypoglycemia. MICRONASE should be used with caution in patients with renal impairment; however, in a single-dose study, plasma clearance of MICRONASE was prolonged only in patients with severe renal impairment.



5. Micronase—for the patient who fails on other diabetic therapy: Potency and dosage flexibility

MICRONASE may prove effective when other drugs fail. Five mg of MICRONASE is approximately equivalent to 250 mg of chlorpropamide or 500 mg of acetohexamide in its ability to lower blood glucose. The dosage range of MICRONASE allows for greater dosage flexibility than other agents.

Overdosage of sulfonylureas, including MICRONASE, can cause hypoglycemia. Although the interpretations are controversial, the UGDP study reported in 1970 that the use of tolbutamide, an oral hypoglycemic drug, was associated with increased cardiovascular mortality.

Upjohn The Upjohn Company Kalamazoo, MI 49001

Your initial Rx in type II diabetes

Micronase®

glyburide, 5 mg Tablets

For brief summary of prescribing information, please turn page.

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DIABETES CARE®

MARCH-APRIL 1985/VOLUME 8/NUMBER 2

Contents

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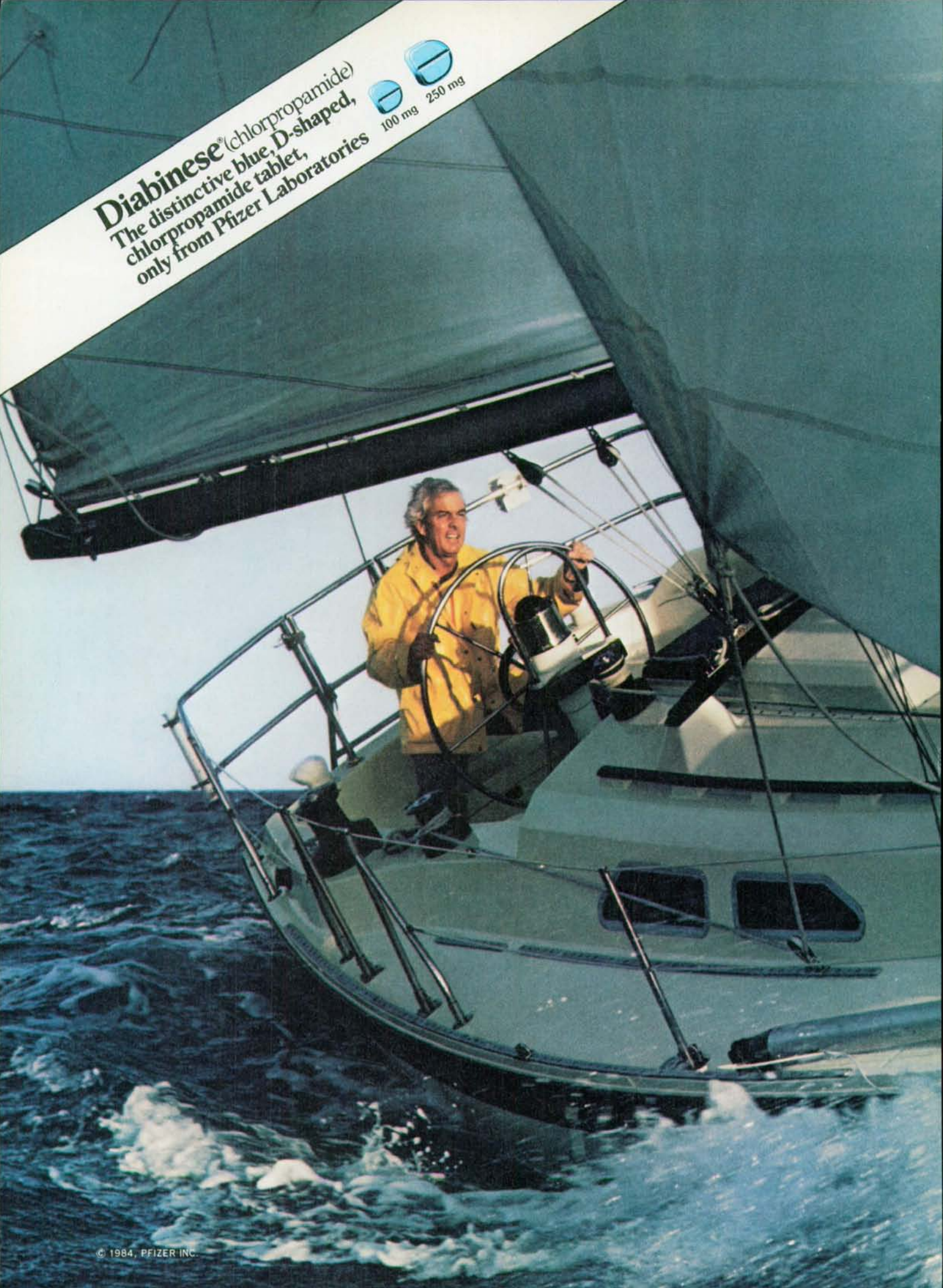

Diabinese®(chlorpropamide)
The distinctive blue, D-shaped,
chlorpropamide tablet,
only from Pfizer Laboratories
100 mg
250 mg
© 1984, PFIZER INC.

Holding Course...

for continued control of the NIDDM patient.

Control of blood sugar requires a day-to-day, week-to-week vigil, particularly when diet alone has failed in NIDDM. Once control has been successfully achieved with diet and Diabinese® (chlorpropamide), the logical course is to continue the regimen.

Diabinese is the most widely prescribed oral diabetic agent in the United States.

As with all sulfonylureas, hypoglycemia may occur with Diabinese, but less frequently than with insulin therapy.

Diabinese effectively controls hyperglycemia...

- known to stimulate beta cells to produce insulin[1,2]
- normalizes hepatic glucose production[2]
- postulated to increase the number of insulin receptors[3]
- postulated to enhance the postreceptor action of insulin[4]

The Diabinese D-Pak helps patients remember and keep track of the convenient once-a-day regimen... which encourages compliance.

To be sure your patients who are controlled on Diabinese continue to receive the familiar blue, D-shaped tablet, specify:

- *Do not substitute,*
- *Medically necessary,* or
- *Dispense as written,*

depending on the state in which you practice.

When diet alone fails...

Diet & Diabinese®

(chlorpropamide) Tablets 100 mg, 250 mg and D-Pak

A proven regimen...continue it with confidence.

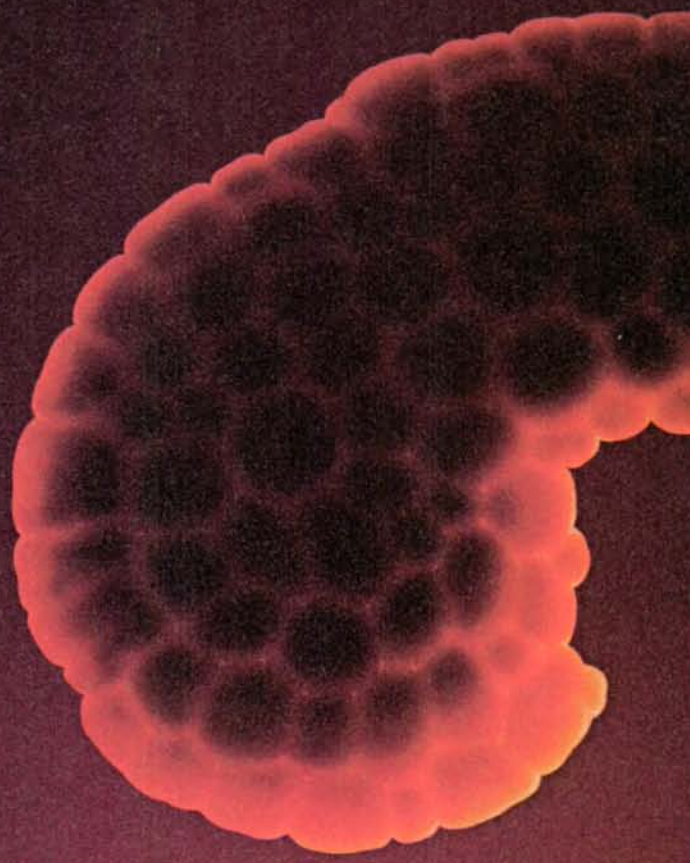
Pfizer LABORATORIES DIVISION
PFIZER INC

Leaders in Oral Diabetic Therapy

Please see references and Diabinese® Brief Summary on following page.

Tolinase® Tablets and diet help put the
(tolazamide)

In most type II diabetic patients, insulin levels may be normal or even elevated, but glucose metabolism is less than normal. Tolinase Tablets pharmacologically influence the way the body metabolizes glucose.



The insulin paradox

The coexistence of normal or elevated insulin levels and elevated glucose levels is a common paradox in patients with type II (non-insulin-dependent) diabetes. This condition suggests a lack of tissue sensitivity to endogenous insulin–a phenomenon many investigators today refer to as cellular insulin resistance.

The failure of normal or above-normal amounts of endogenous insulin to produce a normal response in terms of glucose metabolism is believed to result most often from one or more underlying factors, such as beta-cell defects (inadequate or delayed initial response), defects at the cellular receptor and/or postreceptor level, or hepatic defects.

Initial therapy: A rational approach

Since insulin insufficiency is probably not the basic problem in type II diabetes, diet and exercise are considered the cornerstones of therapy because they help correct the cause of the underutilization of insulin (eg, receptor defect) and may help lower blood glucose. If diet and regular exercise fail to control glucose levels adequately, **Tolinase** Tablets are an appropriate addition to the regimen.

How Tolinase Tablets influence glucose metabolism

The primary mode of action of **Tolinase** Tablets is to lower serum glucose in responsive patients by stimulating the release of additional insulin **(1)**. As therapy continues, it is believed that **Tolinase** promotes peripheral glucose metabolism by helping to correct defects at the cellular receptor **(2)** and postreceptor **(3)** level. In this environment, tissue sensitivity and responsiveness to insulin increase, glucose levels decrease, and insulin levels frequently return toward normal.

Once-a-day dosage with Tolinase Tablets

has been shown to be just as effective as a divided dose in the treatment of non-insulin-dependent diabetes.

Although the interpretations are controversial, the UGDP study reported in 1970 that the use of tolbutamide, an oral hypoglycemia drug, was associated with increased cardiovascular mortality.

As with all sulfonylureas, hypoglycemia may occur. No sulfonylurea should be given to patients with serious kidney, liver, or endocrine disease. **Tolinase** is not indicated in patients with a history of repeated ketoacidosis or coma.

Tolinase® 100, 250 & 500 mg tablets
(tolazamide)

Once a day

For a brief summary of prescribing information, please turn the page.

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001

patient's own insulin back to work.

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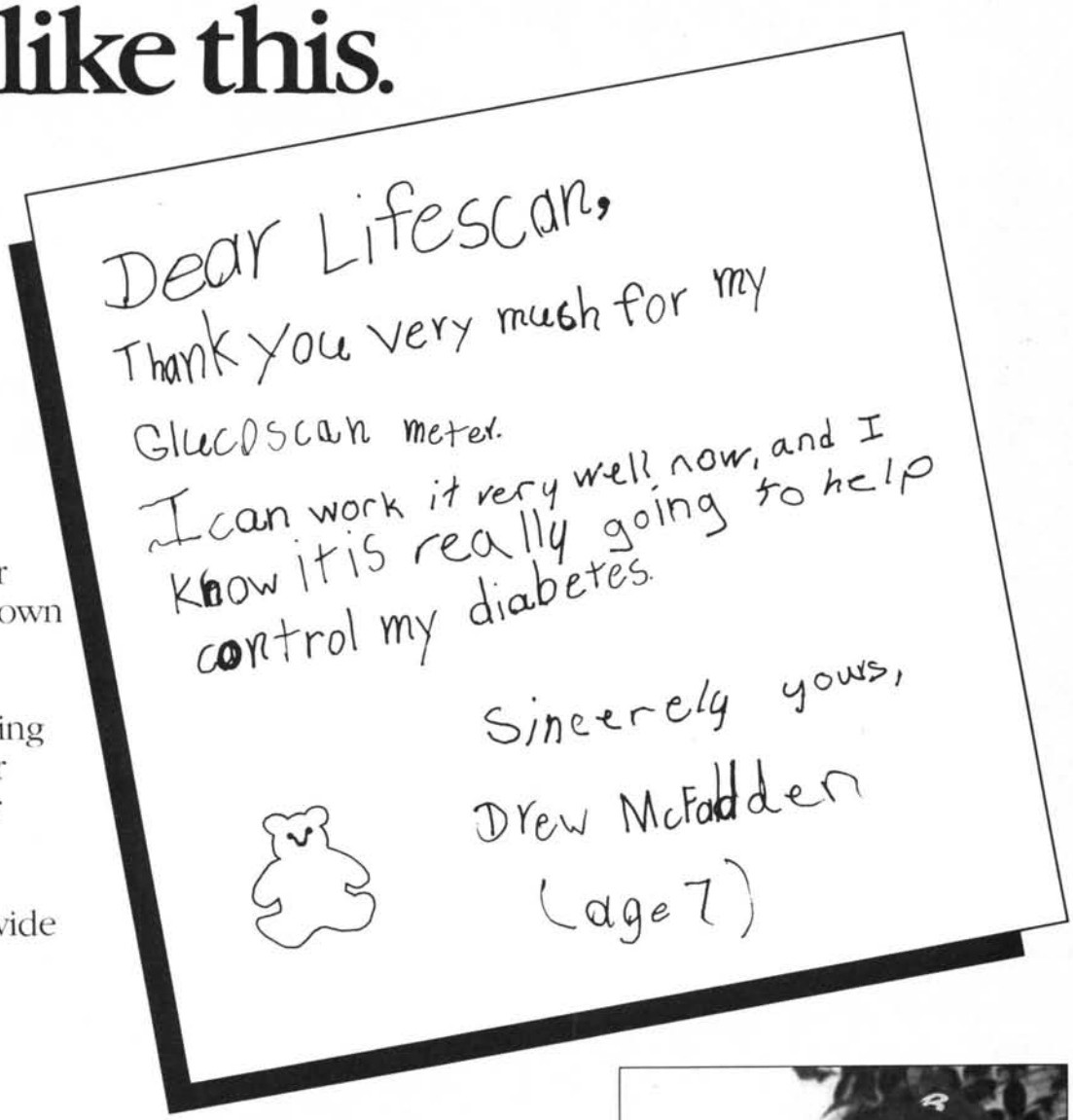

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Drew McFadden and his GLUCOSCAN

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FREE Diabetes '85

The newsletter for people who live with diabetes

Written for the patient with diabetes, **Diabetes '85** is a quarterly, easy-to-read newsletter offering tips on living with diabetes, news updates, recipes, descriptions of common treatment approaches, and sources to turn to for more information.

You can receive office copies of Diabetes '85 by returning this form.

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BRIEF SUMMARY
DIABINESE® (chlorpropamide)
TABLETS, USP

CONTRAINDICATIONS
DIABINESE is contraindicated in patients with:
1. Known hypersensitivity to the drug.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

WARNINGS
SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY
The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes*, 19 (supp. 2):747-830, 1970).
UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in over-all 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 DIABINESE 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.

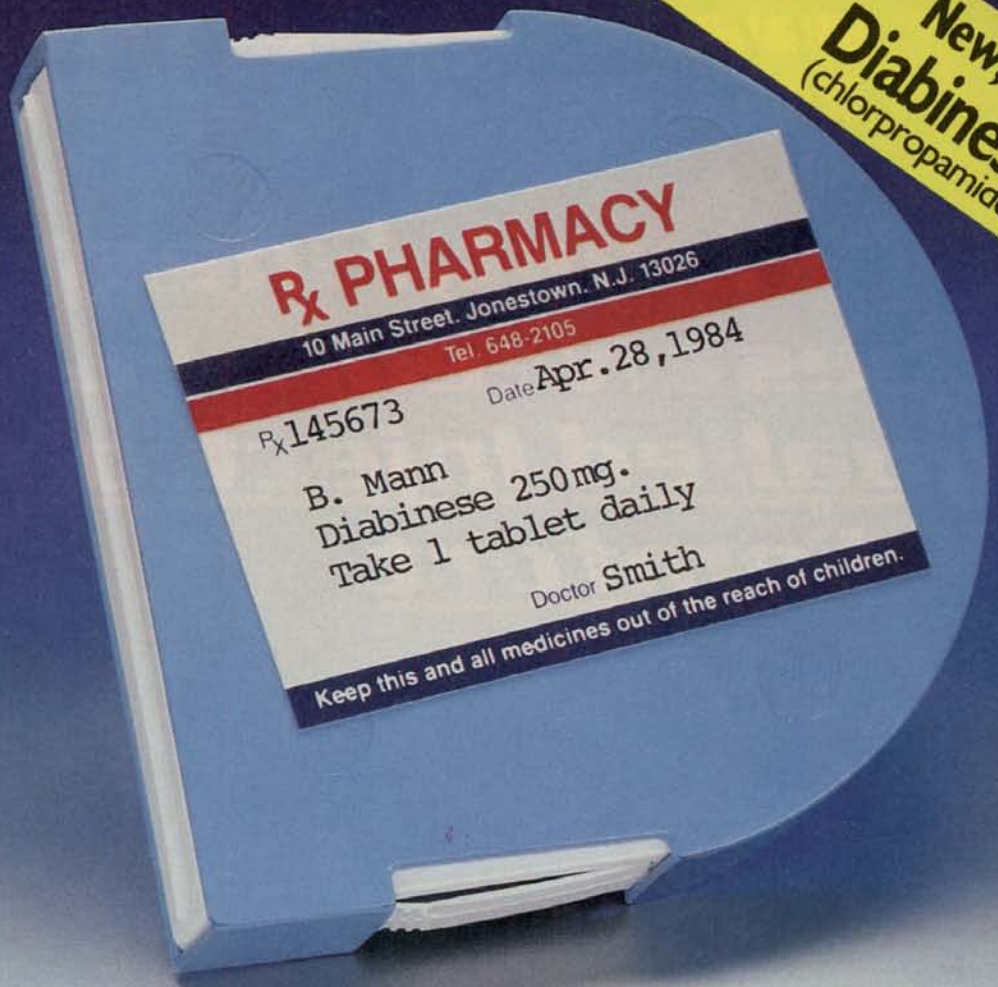
PRECAUTIONS
General
Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may cause elevated blood levels of DIABINESE and the latter may also diminish gluconeogenic capacity, both of which 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 beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.
Because of the long half-life of chlorpropamide, patients who become hypoglycemic during therapy require careful supervision of the dose and frequent feedings for at least 3 to 5 days. Hospitalization and intravenous glucose may be necessary.
Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is 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 DIABINESE and administer insulin.
The effectiveness of any oral hypoglycemic drug, including DIABINESE, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given.

ADVERSE REACTIONS
Hypoglycemia: See PRECAUTIONS section.
Gastrointestinal Reactions: Cholestatic jaundice may occur rarely; DIABINESE should be discontinued if this occurs. Gastrointestinal disturbances are the most common reactions; nausea has been reported in less than 5% of patients, and diarrhea, vomiting, anorexia, and hunger in less than 2%. Other gastrointestinal disturbances have occurred in less than 1% of patients including proctocolitis. They tend to be dose related and may disappear when dosage is reduced.
Dermatologic Reactions: Pruritus has been reported in less than 3% of patients. Other allergic skin reactions, e.g., urticaria and maculopapular eruptions have been reported in approximately 1% or less of patients. These may be transient and may disappear despite continued use of DIABINESE; if skin reactions persist the drug should be discontinued.
Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.
Skin eruptions rarely progressing to erythema multiforme and exfoliative dermatitis have also been reported.
Hematologic Reactions: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, pancytopenia and eosinophilia have been reported with sulfonylureas.
Metabolic Reactions: Hepatic porphyria and disulfiram-like reactions have been reported with DIABINESE.
Endocrine Reactions: On rare occasions, chlorpropamide has caused a reaction identical to the syndrome of inappropriate antidiuretic hormone (ADH) secretion. The features of this syndrome result from excessive water retention and include hyponatremia, low serum osmolality, and high urine osmolity.

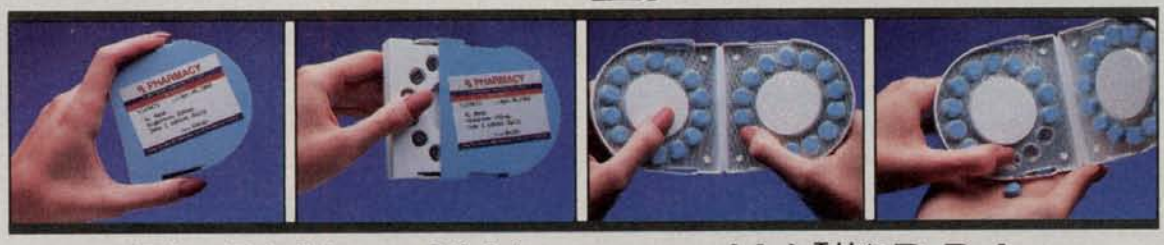
DOSAGE AND ADMINISTRATION
There is no fixed dosage regimen for the management of diabetes mellitus with DIABINESE or any other hypoglycemic agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, and to detect secondary failure. Glycosylated hemoglobin levels may also be of value in monitoring the patient's response to therapy.
The total daily dosage is generally taken at a single time each morning with breakfast. Occasionally cases of gastrointestinal intolerance may be relieved by dividing the daily dosage. A LOADING OR PRIMING DOSE IS NOT NECESSARY AND SHOULD NOT BE USED.
Initial Therapy: 1. The mild to moderately severe, middle-aged, stable, non-insulin-dependent diabetic patient should be started on 250 mg daily. Older patients should be started on smaller amounts of DIABINESE, in the range of 100 to 125 mg daily.
2. No transition period is necessary when transferring patients from other oral hypoglycemic agents to DIABINESE. The other agent may be discontinued abruptly and chlorpropamide started at once. In prescribing chlorpropamide, due consideration must be given to its greater potency.
Many mild to moderately severe, middle-aged, stable non-insulin-dependent diabetic patients receiving insulin can be placed directly on the oral drug and their insulin abruptly discontinued. For patients requiring more than 40 units of insulin daily, therapy with DIABINESE may be initiated with a 50 per cent reduction in insulin for the first few days, with subsequent further reductions dependent upon the response.
Five to seven days after the initial therapy, the blood level of chlorpropamide reaches a plateau. Dosage may subsequently be adjusted upward or downward by increments of not more than 50 to 125 mg at intervals of three to five days to obtain optimal control. More frequent adjustments are usually undesirable.
Maintenance Therapy: Most moderately severe, middle-aged, stable non-insulin-dependent diabetic patients are controlled by approximately 250 mg daily. Many investigators have found that some milder diabetics do well on daily doses of 100 mg or less. Many of the more severe diabetics may require 500 mg daily for adequate control. PATIENTS WHO DO NOT RESPOND COMPLETELY TO 500 MG DAILY WILL USUALLY NOT RESPOND TO HIGHER DOSES. MAINTENANCE DOSES ABOVE 750 MG DAILY SHOULD BE AVOIDED.
SUPPLY: Blue, 'D'-shaped, scored tablets in strengths of 100 mg, tablet code 393; (100's, NDC# 0663-3930-66; 500's, NDC# 0663-3930-73; and 100 unit dose of 10 x 10, NDC# 0663-3930-41) and 250 mg, tablet code 394; (100's, NDC# 0663-3940-66; 250's, NDC# 0663-3940-71, 1000's, NDC# 0663-3940-82; 100 unit dose of 10 x 10, NDC# 0663-3940-41; and 28's D-Pak, NDC# 0663-3940-28).
RECOMMENDED STORAGE: Store below 86°F (30°C).
CAUTION: Federal law prohibits dispensing without prescription.

Pfizer
LABORATORIES DIVISION
PFIZER INC.

New, Improved
Diabinese® D-Pak
(chlorpropamide) Tablets 250 mg



The Case for Compliance



The Diabinese® (chlorpropamide) Tablets 250 mg D-Pak: A convenient way for patients to remember and keep track of every once-a-day dose. Now easier to use.

The Diabinese D-Pak (dispenser pack) contains a full 4-week supply of Diabinese 250-mg tablets in a lightweight, D-shaped, compact case. Inside, the distinctive blue, D-shaped tablets are arranged in easy-to-follow circles under clear day-of-the-week headings. So it is almost impossible to accidentally skip or repeat a dose. The blister packaging has been improved so tablets are easier to remove. The Diabinese D-Pak is particularly beneficial to the newly diagnosed NIDDM patient who is a dietary failure, since compliance with a new therapeutic regimen can be a problem.

Next time you prescribe Diabinese 250 mg *q.d.* specify the

Diabinese® D-Pak
(chlorpropamide) Tablets 250 mg

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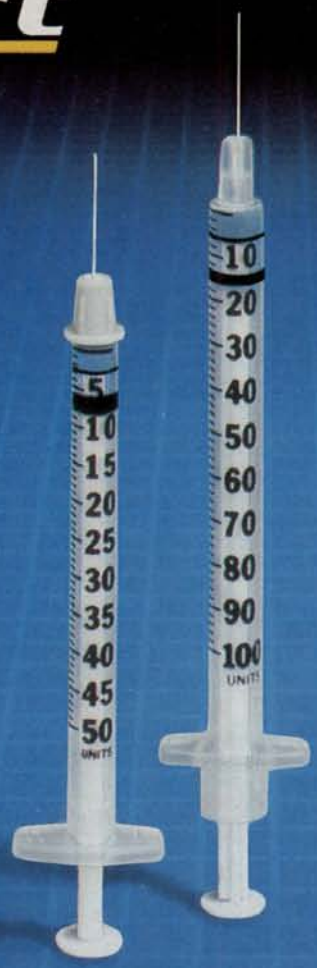
Please see Diabinese® (chlorpropamide) brief summary on preceding page.

B-D MICRO-FINE® III

The Thinnest, Finest, Sharpest Needle For Unequalled Injection Comfort



The Best There Is.

The needle on every other insulin syringe has been surpassed by the advanced B-D MICRO-FINE III needle... a unique achievement in injection comfort.

Tests with hundreds of insulin users prove conclusively that they have never before experienced such ease with their injections. Some typical comments: "It's like no injection at all"..."It's a much easier injection".

Finest Insulin Syringe Needle Ever Made.

MICRO-FINE III is made with the highest quality surgical-grade stainless steel...tempered and honed to incredible fineness and strength. Result: the thinnest, finest, sharpest needle for unequalled injection comfort.

MICRO-BONDED® Lubrication For Extra Comfort.

An exclusive B-D process keeps the lubrication on the needle even after it has pierced the insulin vial stopper—and, during the injection—for smoother, more effortless injections.

America's Most Recommended Syringes.

Doctors, nurses and pharmacists recommend B-D syringes above all others. And B-D syringes are used most in hospitals—trusted most by insulin users.

The B-D MICRO-FINE III Needle — Overwhelmingly Preferred By Insulin Users For *Unequalled Injection Comfort*

B-D Better Diabetes Care

B-D ANNOUNCES BLOOD SAMPLING WITH VIRTUALLY NO PAIN

NEW!

B-D MICRO-FINE™ LANCET

Virtually painless—thinnest, sharpest lancet for maximum comfort.

NEW!

B-D MICRO-FINE™ LANCETS

- Virtually painless. MICRO-FINE LANCET has the thinnest, sharpest point available for maximum comfort.
- Easy to hold and use. Flat shape and special finger-grip design make lancing simple and sure...prevent slipping or twisting of lancet.
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NEW!

B-D AUTOLANCE™

Fully automatic...simple and easy to use.

NEW!

B-D AUTOLANCE™

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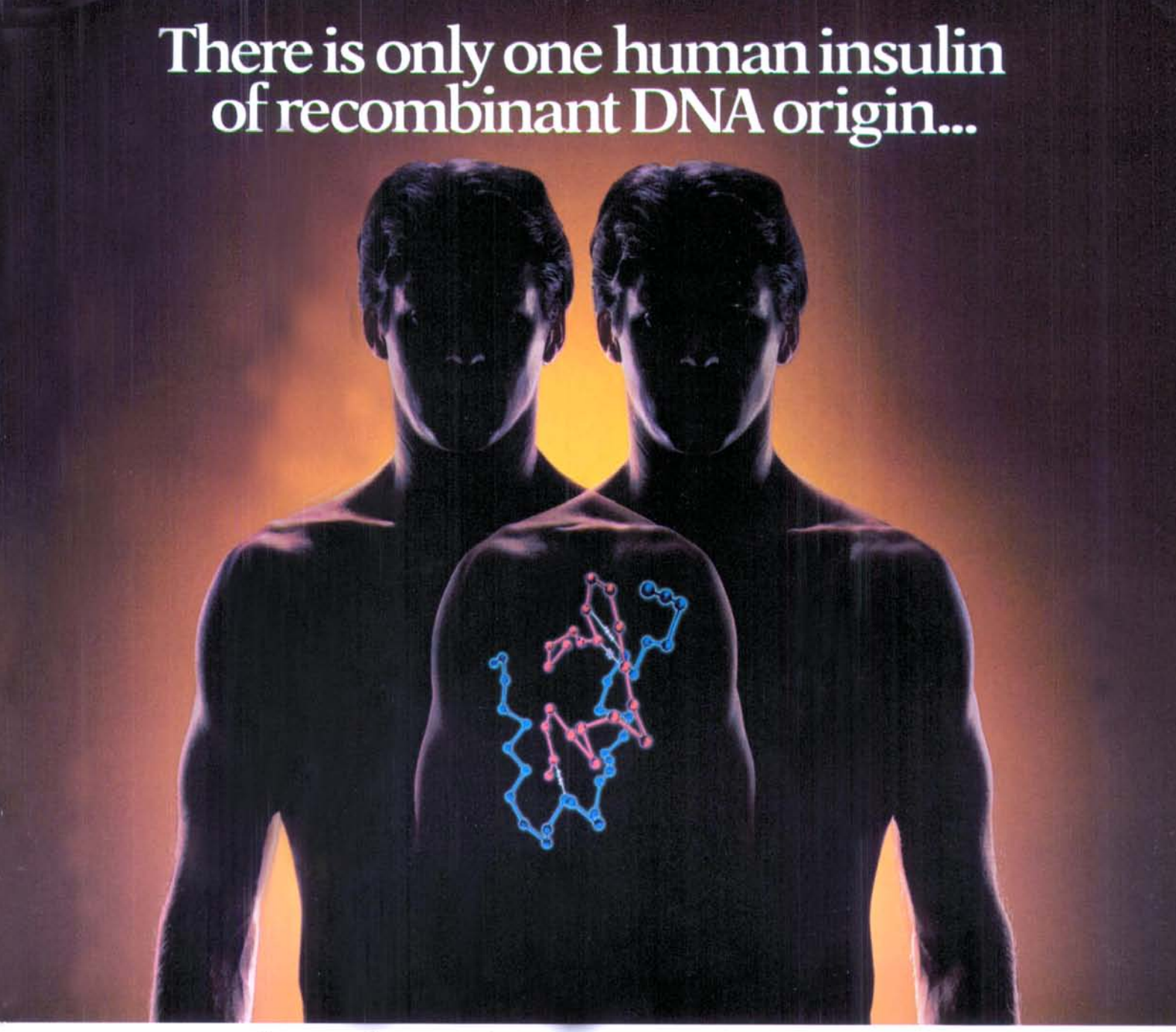
- Compact, convenient, attractive design.
- Lancet is out of sight to reduce anxiety.

B-D Better Diabetes Care

There is only one human insulin of recombinant DNA origin...



and it is identical to natural human insulin

From Lilly, a leader in diabetes care for six decades, there is now available the first and only insulin *not* derived from beef or pork pancreases—Humulin® (human insulin [recombinant DNA origin]).

In multicenter studies completed to date, Humulin was shown to be less immunogenic than mixed beef-pork or purified pork insulin. The clinical significance of these data has not yet been demonstrated.

Available in two forms: rapid-acting *Humulin® R* (regular human insulin [recombinant DNA origin], Injection) and intermediate-acting *Humulin® N* (NPH human insulin [recombinant DNA origin], Isophane Suspension).

Humulin®
human insulin
(recombinant DNA origin)

Lilly Leadership IN DIABETES CARE

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN REFINEMENT, PURITY, STRENGTH, BRAND (MANUFACTURER), TYPE (REGULAR, NPH, LENTE®, ETC.), AND/OR METHOD OF MANUFACTURE (RECOMBINANT DNA VERSUS ANIMAL-SOURCE INSULIN) MAY RESULT IN THE NEED FOR A CHANGE IN DOSAGE.

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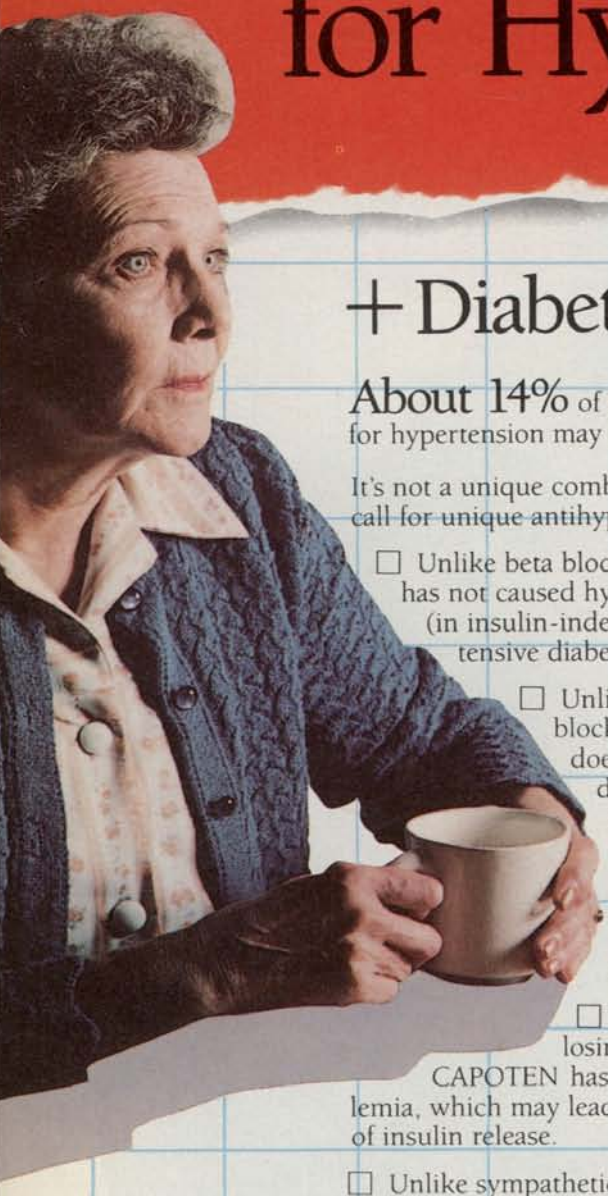
*Angiotensin Converting Enzyme

Capoten® (captopril tablets) for Hypertension†-Plus...



+ Diabetes†

About 14% of patients treated for hypertension may also have diabetes.[1]

It's not a unique combination. But it can call for unique antihypertensive therapy.

☐ Unlike beta blockers,[2,3] CAPOTEN has not caused hyperglycemia (in insulin-independent hypertensive diabetics).

☐ Unlike some beta blockers,[2,3] CAPOTEN does not mask the dizziness and sweating often occurring with hypoglycemia (in insulin-dependent hypertensive diabetics).

☐ Unlike potassium-losing diuretics,[2,3] CAPOTEN has not caused hypokalemia, which may lead to suppression of insulin release.

☐ Unlike sympathetic inhibitors,[3] CAPOTEN rarely affects sexual potency (which may already be compromised in diabetic men).

Please see Precautionary Guidelines for use of CAPOTEN and brief summary of prescribing information, especially the INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS sections on last pages of this advertisement.

+ Bronchospastic pulmonary disease†

About 7% of patients treated for hypertension may also have asthma.[1]

A problem that may call for an uncommon antihypertensive solution.

☐ CAPOTEN rarely causes bronchospasm.[4]

SQUIBB

+ Heart failure†

Approximately 13%

of patients treated for hypertension may also have heart failure.[1]

Moreover, the Framingham study demonstrated that 75% of patients with heart failure previously had been hypertensive.[15] The two disorders may share a common link. They do share a common therapy.

☐ Unlike beta blockers, CAPOTEN lowers blood pressure without the associated decrease in heart rate and cardiac output.

☐ Unlike any other antihypertensive agent, CAPOTEN blocks activation of the renin-angiotensin-aldosterone (RAA) system, which may play a role in both heart failure and hypertension.

†CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or have developed unacceptable side effects.
‡Systolic ≥ 160 mm Hg and diastolic ≥ 95 mm Hg in two readings.

ACE*-INHIBITOR

Capoten®
(captopril tablets)

The Unique Solution for the Hypertension-Plus Patient

*Angiotensin Converting Enzyme

ACE* INHIBITOR

Capoten®
(captopril tablets)

Precautionary Guidelines

CAPOTEN has been associated with the development of neutropenia/agranulocytosis (0.3% of 4,000 patients) or proteinuria (1.2% of 4,000 patients).† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the autoimmune response.

The following precautionary guidelines are recommended for all patients receiving CAPOTEN:

☐ Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.

☐ Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.

☐ Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.

☐ The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.

*Angiotensin Converting Enzyme

†Please see the following brief summary of prescribing information for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

References:

1. Market Measures Inc.: Treatment of Hypertension V, February 1983.
2. Christlieb AR: Management of hypertension in the patient with diabetes mellitus. Practical Cardiol 8:94-103, 1982.
3. Christlieb AR: Diabetes and hypertension. Cardiovasc Rev Reports 1:609-616, 1980.
4. Data on file, Squibb Institute for Medical Research.
5. McKee PA, Castelli WP, McNamara PM, et al: The natural history of heart failure: The Framingham study. N Engl J Med 285:1441-1446, 1971.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension—Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Proteinuria—Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine—the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis—Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform 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.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may 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.

PRECAUTION: General: *Impaired Renal Function,* Hypertension—Some hypertensive 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 with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *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 major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours 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. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.

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.

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. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

(Continued on next page)

(Continued from preceding page)

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril 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 about 4000 patients.

Renal—One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic—Rash (usually mild, maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—About 7 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). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern in correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN should be taken one hour before meals. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function. **Consult package insert before prescribing CAPOTEN (captopril).**

HOW SUPPLIED: Available in tablets of 25, 50, and 100 mg in bottles of 100, and in UNIMATIC® unit-dose packs of 100 tablets.

Princeton, NJ 08540 525-552
Issued: January 1985

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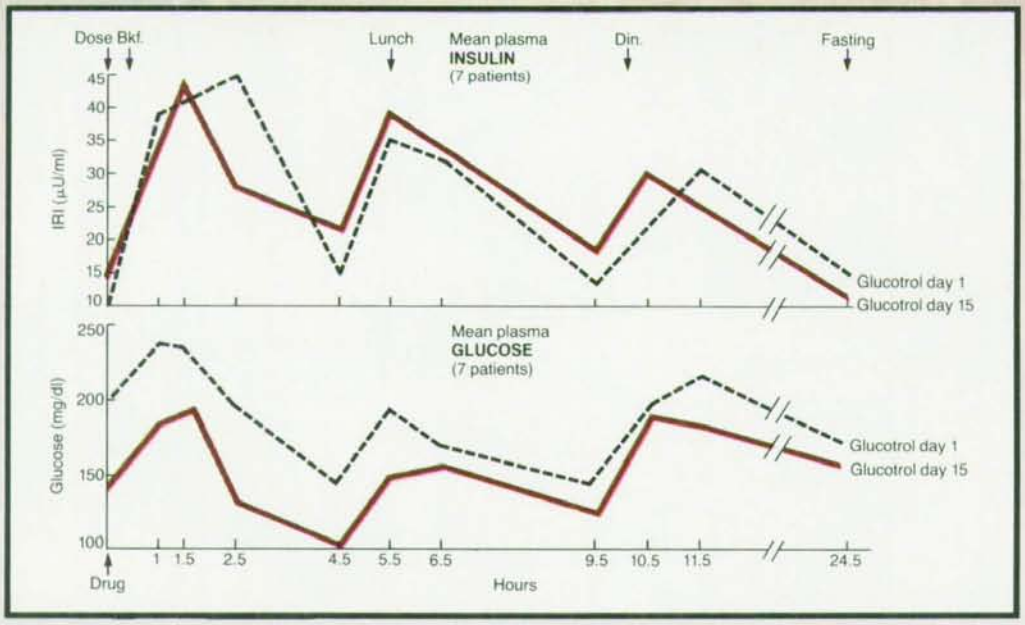

(Adapted from Peterson CM, et al[1])

Glucose and insulin response to three standard meals was measured at eleven time points on the first and fifteenth days of administration of Glucotrol (glipizide) to seven patients with NIDDM. The mean dose of Glucotrol was 8.7 mg per day (0.1 mg/kg).

■ Insulin levels rose markedly after the first meal, then dropped, then rose again following subsequent meals.

■ The insulin response pattern with Glucotrol closely simulates the pattern commonly seen in nondiabetics.

References: 1. Peterson CM, Sims RV, Jones RL, et al: Bioavailability of glipizide and its effect on blood glucose and insulin levels in patients with non-insulin-dependent diabetes. *Diabetes Care* 1982; 5:497-500. **2.** Melander A, Wåhlin-Boll E: Clinical pharmacology of glipizide, in *Proceedings of a Symposium: New Perspectives in Noninsulin-Dependent Diabetes Mellitus and the Role of Glipizide in Its Treatment. Am J Med*, pp. 41-45, Nov. 30, 1983. **3.** Feinglos MN, Lebovitz HE: Long-term safety and efficacy of glipizide, in *Proceedings of a Symposium: New Perspectives in Noninsulin-Dependent Diabetes Mellitus and the Role of Glipizide in Its Treatment. Am J Med*, pp. 60-66, Nov. 30, 1983.

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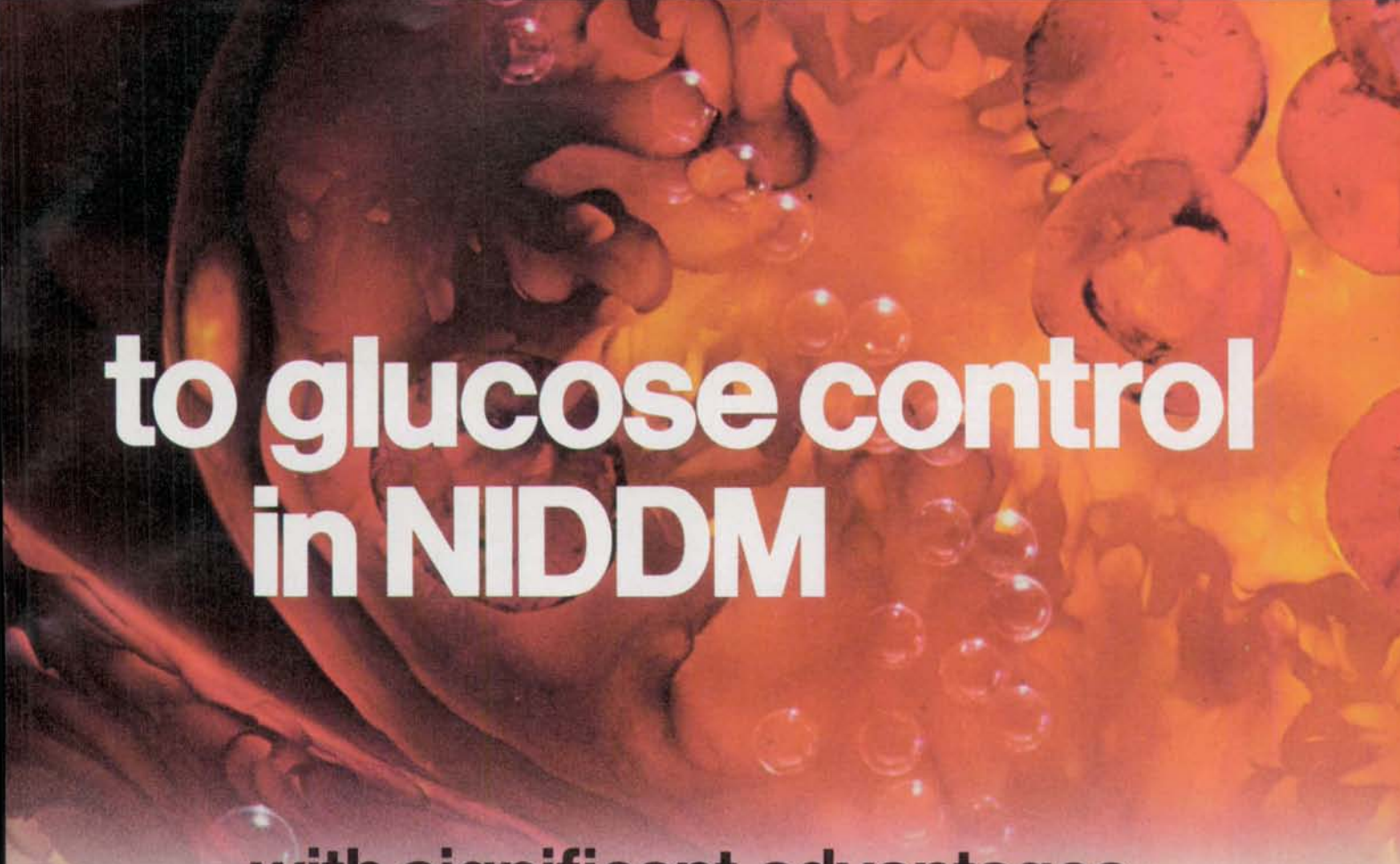


to glucose control in NIDDM

with significant advantages for many NIDDM patients

Rapid, consistent therapeutic action "The aim of sulfonylurea treatment should be complete normalization of glucose economy... therefore, the sulfonylurea should be potent and rapid-acting. Moreover, it should have complete bioavailability in order to minimize variations between and within individual subjects.

"Glipizide [Glucotrol] has complete bioavailability and its absorption and onset of action are very rapid."[2]

Rapid excretion, inactive metabolites "As glipizide [Glucotrol] is very rapidly eliminated, and as there is no evidence that its metabolites are significantly active, the risk of long-lasting hypoglycemia should be small.... "[2] However, as with all sulfonylureas, hypoglycemia may occur.

Long-term metabolic improvement "Long-term therapy with glipizide, in contrast to studies of other sulfonylureas, often results in a sustained increase in glucose-stimulated insulin secretion."[3]

While controversy remains in the findings of the UGDP, there have been reports of increased cardiovascular risk associated with oral hypoglycemic therapy.

Glucotrol®

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

When diet alone fails in non-insulin-dependent diabetes mellitus

Please turn page for Glucotrol® (glipizide) prescribing information.

References: 1. Peterson CM, Sims RV, Jones RL, et al: Bioavailability of glipizide and its effect on blood glucose and insulin levels in patients with non-insulin-dependent diabetes. *Diabetes Care* 1982; 5:497-500. 2. Melander A, Wåhlin-Boll E: Clinical pharmacology of glipizide, in *Proceedings of a Symposium: New Perspectives in Noninsulin-Dependent Diabetes Mellitus and the Role of Glipizide in Its Treatment. Am J Med*, pp. 41-45, Nov. 30, 1983. 3. Feinglos MN, Lebovitz HE: Long-term safety and efficacy of glipizide, in *Proceedings of a Symposium: New Perspectives in Noninsulin-Dependent Diabetes Mellitus and the Role of Glipizide in Its Treatment. Am J Med*, pp. 60-66, Nov. 30, 1983.

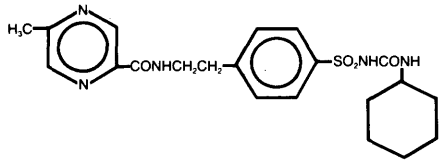
GLUCOTROL® (glipizide) TABLETS

For Oral Use

DESCRIPTION

GLUCOTROL (glipizide) is an oral blood-glucose-lowering drug of the sulfonylurea class.

The Chemical Abstracts name of glipizide is 1-cyclohexyl-3-[[p-[2-(5-methylpyrazinecarboxamido)ethyl]phenyl]sulfonyl]urea. The molecular formula is $C_{21}H_{27}N_5O_4S$; the molecular weight is 445.55; the structural formula is shown below:



Glipizide is a whitish, odorless powder with a melting point of 201-207°C (dec.) and a pKa of 5.9. It is insoluble in water and alcohols, but soluble in 0.1 *N* NaOH; it is freely soluble in dimethylformamide. GLUCOTROL tablets for oral use are available in 5 and 10 mg strengths.

CLINICAL PHARMACOLOGY

Mechanism of Action: The primary mode of action of GLUCOTROL in experimental animals appears to be the stimulation of insulin secretion from the beta cells of pancreatic islet tissue and is thus dependent on functioning beta cells in the pancreatic islets. In humans GLUCOTROL appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which GLUCOTROL lowers blood glucose during long-term administration has not been clearly established. In man, stimulation of insulin secretion by GLUCOTROL in response to a meal is undoubtedly of major importance. Fasting insulin levels are not elevated even on long-term GLUCOTROL administration, but the postprandial insulin response continues to be enhanced after at least 6 months of treatment. The insulinotropic response to a meal occurs within 30 minutes after an oral dose of GLUCOTROL in diabetic patients, but elevated insulin levels do not persist beyond the time of the meal challenge. Extrapancreatic effects may play a part in the mechanism of action of oral sulfonylurea hypoglycemic drugs.

Blood sugar control persists in some patients for up to 24 hours after a single dose of GLUCOTROL, even though plasma levels have declined to a small fraction of peak levels by that time (see Pharmacokinetics below).

Some patients fail to respond initially, or gradually lose their responsiveness to sulfonylurea drugs, including GLUCOTROL. Alternatively, GLUCOTROL may be effective in some patients who have not responded or have ceased to respond to other sulfonylureas.

Other Effects: It has been shown that GLUCOTROL therapy was effective in controlling blood sugar without deleterious changes in the plasma lipoprotein profiles of patients treated for NIDDM.

In a placebo-controlled, crossover study in normal volunteers, GLUCOTROL had no antidiuretic activity, and, in fact, led to a slight increase in free water clearance.

Pharmacokinetics: Gastrointestinal absorption of GLUCOTROL in man is uniform, rapid, and essentially complete. Peak plasma concentrations occur 1-3 hours after a single oral dose. The half-life of elimination ranges from 2-4 hours in normal subjects, whether given intravenously or orally. The metabolic and excretory patterns are similar with the two routes of administration, indicating that first-pass metabolism is not significant. GLUCOTROL does not accumulate in plasma on repeated oral administration. Total absorption and disposition of an oral dose was unaffected by food in normal volunteers, but absorption was delayed by about 40 minutes. Thus GLUCOTROL was more effective when administered about 30 minutes before, rather than with, a test meal in diabetic patients. Protein binding was studied in serum from volunteers who received either oral or intravenous GLUCOTROL and found to be 98-99% one hour after either route of administration. The apparent volume of distribution of GLUCOTROL after intravenous administration was 11 liters, indicative of localization within the extracellular fluid compartment. In mice no GLUCOTROL or metabolites were detectable autoradiographically in the brain or spinal cord of males or females, nor in the fetuses of pregnant females. In another study, however, very small amounts of radioactivity were detected in the fetuses of rats given labelled drug.

The metabolism of GLUCOTROL is extensive and occurs mainly in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Less than 10% unchanged GLUCOTROL is found in the urine.

INDICATIONS AND USAGE

GLUCOTROL is indicated as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with non-insulin-dependent diabetes mellitus (NIDDM; type II), formerly known as maturity-onset diabetes, after an adequate trial of dietary therapy has proved unsatisfactory.

In initiating treatment for non-insulin-dependent diabetes, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified, and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered. Use of GLUCOTROL must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone also may be transient, thus requiring only short-term administration of GLUCOTROL.

During maintenance programs, GLUCOTROL should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations.

In considering the use of GLUCOTROL in asymptomatic patients, it should be recognized that controlling the 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

GLUCOTROL is contraindicated in patients with:

1. Known hypersensitivity to the drug.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

WARNINGS

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

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

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

PRECAUTIONS

General

Renal and Hepatic Disease: The metabolism and excretion of GLUCOTROL may be slowed in patients with impaired renal and/or hepatic function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may cause elevated blood levels of GLUCOTROL and the latter may also diminish gluconeogenic capacity, both of which 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 beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of Control of Blood Glucose: When a patient stabilized on any diabetic regimen is 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 GLUCOTROL and administer insulin.

The effectiveness of any oral hypoglycemic drug, including GLUCOTROL, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given.

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

Information for Patients: Patients should be informed of the potential risks and advantages of GLUCOTROL and of alternative modes of therapy. They should also be informed about the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving GLUCOTROL, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving GLUCOTROL, the patient should be observed closely for loss of control. *In vitro* binding studies with human serum proteins indicate that GLUCOTROL binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to the clinical situation and in the use of GLUCOTROL with these drugs.

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. When such drugs are administered to a patient receiving GLUCOTROL, the patient should be closely observed for loss of control. When such drugs are withdrawn from a patient receiving GLUCOTROL, the patient should be observed closely for hypoglycemia.

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

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

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

Nonteratogenic Effects: Prolonged severe hypoglycemia (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 with the use of agents with prolonged half-lives. If GLUCOTROL is used during pregnancy, it should be discontinued at least one month before the expected delivery date.

Nursing Mothers: Although it is not known whether GLUCOTROL is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, 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. If the drug is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

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

ADVERSE REACTIONS

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

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

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

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

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

Metabolic: Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas. In the mouse, GLUCOTROL pretreatment did not cause an accumulation of acetaldehyde after ethanol administration. Clinical experience to date has shown that GLUCOTROL has an extremely low incidence of disulfiram-like alcohol reactions.

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

Laboratory Tests: The pattern of laboratory test abnormalities observed with GLUCOTROL was similar to that for other sulfonylureas. Occasional mild to moderate elevations of SGOT, LDH, alkaline phosphatase, BUN and creatinine were noted. One case of jaundice was reported. The relationship of these abnormalities to GLUCOTROL is uncertain, and they have rarely been associated with clinical symptoms.

OVERDOSAGE

There is no well documented experience with GLUCOTROL overdosage. The acute oral toxicity was extremely low in all species tested (LD_{50} greater than 4 g/kg).

Overdosage of sulfonylureas including GLUCOTROL can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological 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 since hypoglycemia may recur after apparent clinical recovery. Clearance of GLUCOTROL from plasma would be prolonged in persons with liver disease. Because of the extensive protein binding of GLUCOTROL(glipizide), dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOTROL or any other hypoglycemic agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of an adequate blood-glucose-lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels may also be of value in monitoring the patient's response to therapy.

Short-term administration of GLUCOTROL may be sufficient during periods of transient loss of control in patients usually controlled well on diet.

In general, GLUCOTROL should be given approximately 30 minutes before a meal to achieve the greatest reduction in postprandial hyperglycemia.

Initial Dose: The recommended starting dose is 5 mg, given before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg.

Titration: Dosage adjustments should ordinarily be in increments of 2.5-5 mg, as determined by blood glucose response. At least several days should elapse between titration steps. If response to a single dose is not satisfactory, dividing that dose may prove effective. The maximum recommended once daily dose is 15 mg. Doses above 15 mg should ordinarily be divided and given before meals of adequate caloric content. The maximum recommended total daily dose is 40 mg.

Maintenance: Some patients may be effectively controlled on a once-a-day regimen, while others show better response with divided dosing. Total daily doses above 15 mg should ordinarily be divided. Total daily doses above 30 mg have been safely given on a b.i.d. basis to long-term patients.

In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions (see PRECAUTIONS section).

Patients Receiving Insulin: As with other sulfonylurea-class hypoglycemics, many stable non-insulin-dependent diabetic patients receiving insulin may be safely placed on GLUCOTROL. When transferring patients from insulin to GLUCOTROL, the following general guidelines should be considered:

For patients whose daily insulin requirement is 20 units or less, insulin may be discontinued and GLUCOTROL therapy may begin at usual dosages. Several days should elapse between GLUCOTROL titration steps.

For patients whose daily insulin requirement is greater than 20 units, the insulin dose should be reduced by 50% and GLUCOTROL therapy may begin at usual dosages. Subsequent reductions in insulin dosage should depend on individual patient response. Several days should elapse between GLUCOTROL titration steps.

During the insulin withdrawal period, the patient should test urine samples for sugar and ketone bodies at least three times daily. Patients should be instructed to contact the prescriber immediately if these tests are abnormal. In some cases, especially when patient has been receiving greater than 40 units of insulin daily, it may be advisable to consider hospitalization during the transition period.

Patients Receiving Other Oral Hypoglycemic Agents: As with other sulfonylurea-class hypoglycemics, no transition period is necessary when transferring patients to GLUCOTROL. Patients should be observed carefully (1-2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (e.g., chlorpropamide) to GLUCOTROL due to potential overlapping of drug effect.

HOW SUPPLIED

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

RECOMMENDED STORAGE: Store below 86°F (30°C).

CAUTION: Federal law prohibits dispensing without prescription.

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