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diabetes

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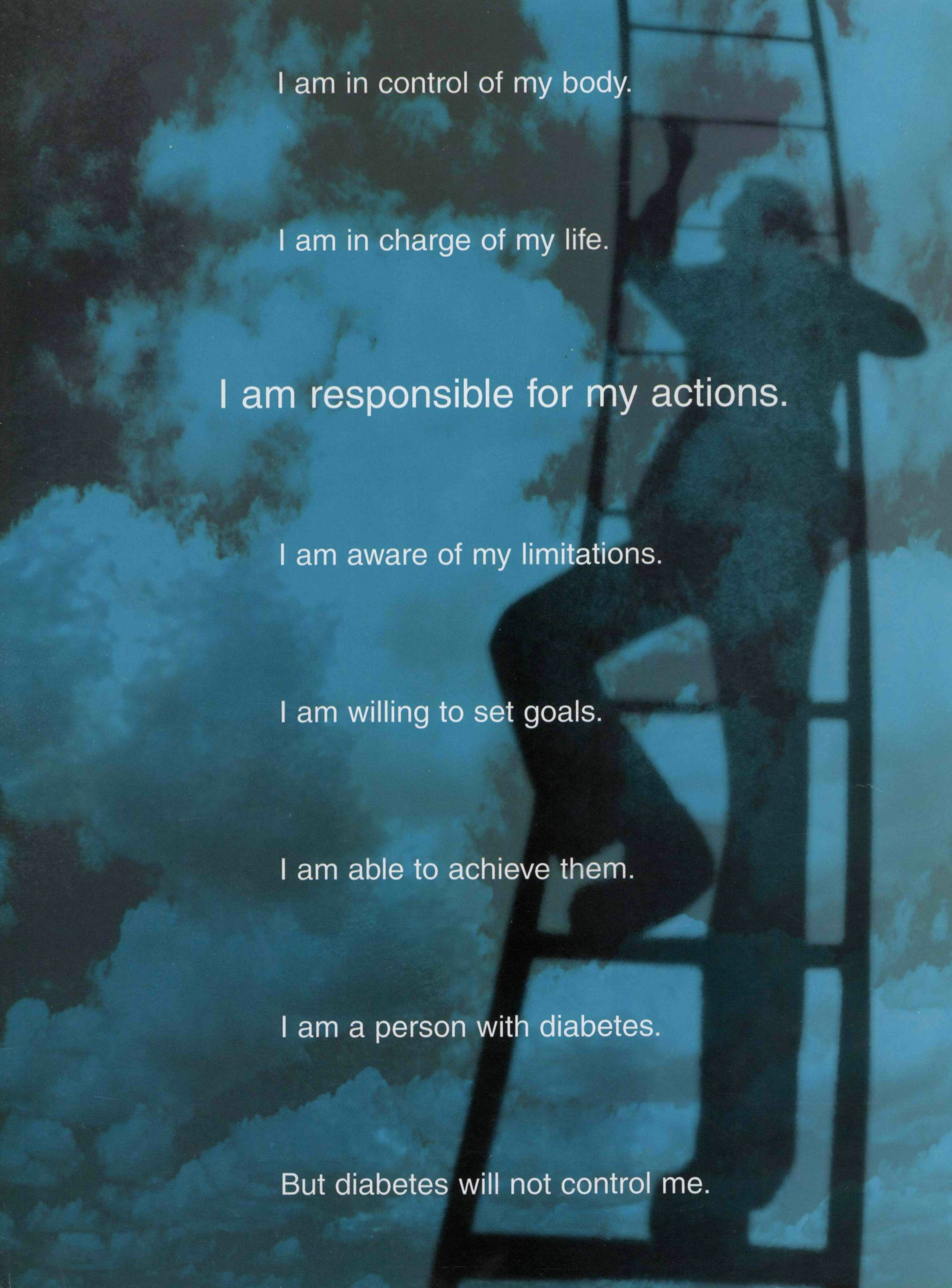
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I am in charge of my life.
I am responsible for my actions.
I am aware of my limitations.
I am willing to set goals.
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I am a person with diabetes.
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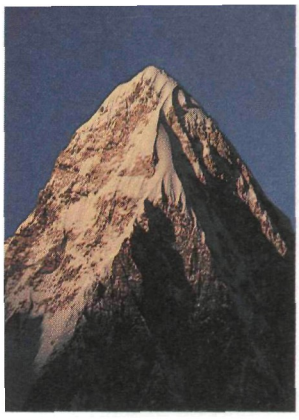

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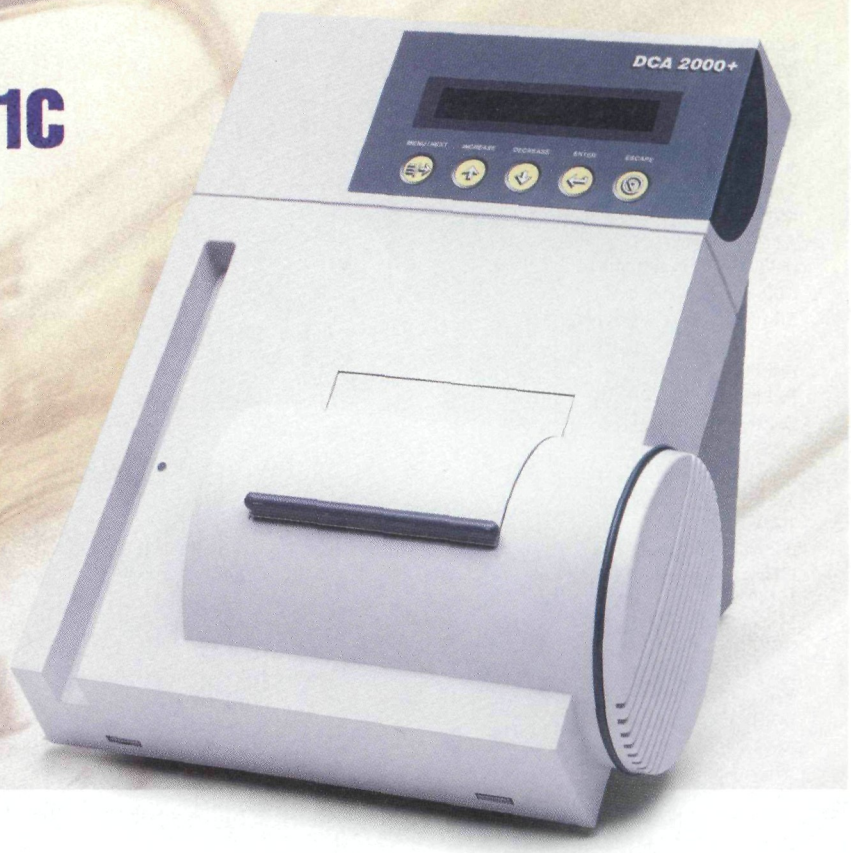

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REFERENCE:

1. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993; 329:977-986.

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All manuscripts and other editorial correspondence should be sent to the editor, Gordon C. Weir, MD, *Diabetes* Editorial Office, Joslin Diabetes Center, One Joslin Place, Boston, MA 02215; (617) 735-1930.

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Manuscripts should be prepared in accordance with the requirements specified in the document "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," *New England Journal of Medicine* 336:309–315, 1997. "Instructions for Authors" containing specifications for manuscript preparation appears in the January and July issues of *Diabetes*.

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A first-line, first-choice sulfonylurea for type 2 diabetes as an adjunct to diet and exercise

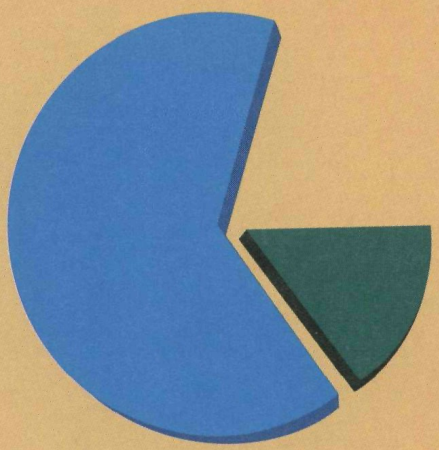
ONCE-A-DAY

Amaryl®

glimepiride TABLETS

INSULIN-SPARING GLUCOSE CONTROL

Amaryl achieved tight control ($HbA_{1c} \leq 7.2\%$) as defined by the DCCT[1,2]

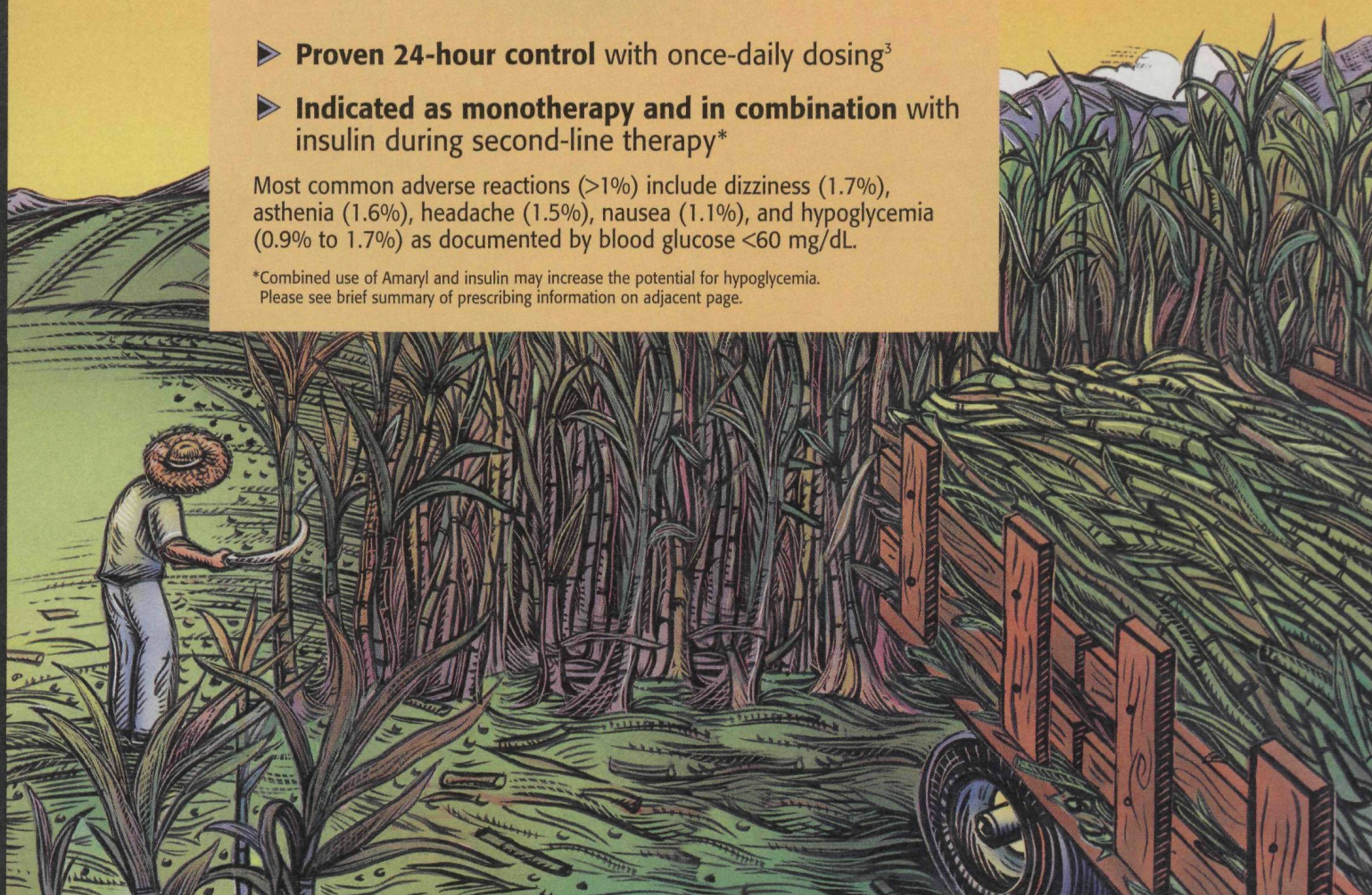


(n=247)

- **Proven 24-hour control** with once-daily dosing[3]
- **Indicated as monotherapy and in combination** with insulin during second-line therapy*

Most common adverse reactions (>1%) include dizziness (1.7%), asthenia (1.6%), headache (1.5%), nausea (1.1%), and hypoglycemia (0.9% to 1.7%) as documented by blood glucose <60 mg/dL.

*Combined use of Amaryl and insulin may increase the potential for hypoglycemia.
Please see brief summary of prescribing information on adjacent page.



Brief Summary of
Prescribing Information as of November 1996

Amaryl®

glimepiride• TABLETS

1, 2, and 4 mg

Drug Interactions. The hypoglycemic action of sulfonylureas may be *potentiated by certain drugs, including nonsteroidal anti-inflammatory* drugs and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When these drugs are administered to a patient receiving AMARYL®, the patient should be observed closely for hypoglycemia. When these drugs are withdrawn from a patient receiving AMARYL®, the patient should be observed closely for loss of glycemic control.

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, and isoniazid. When these drugs are administered to a patient receiving AMARYL®, the patient should *be closely observed for loss of control. When these drugs are withdrawn* from a patient receiving AMARYL®, the patient should be observed closely for hypoglycemia.

Coadministration of aspirin (1 g tid) and AMARYL® led to a 34% decrease in the mean glimepiride AUC and, therefore, a 34% increase in the mean CL/f. The mean C_{max} had a decrease of 4%. Blood glucose and serum C-peptide concentrations were unaffected and no hypoglycemic symptoms were reported. Pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of aspirin and other salicylates.

Coadministration of either cimetidine (800 mg once daily) or ranitidine (150 mg bid) with a single 4-mg oral dose of AMARYL® did not significantly alter the absorption and disposition of glimepiride, and no differences were *seen in hypoglycemic symptomatology. Pooled data from clinical trials* showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of H2-receptor antagonists.

Concomitant administration of propranolol (40 mg tid) and AMARYL® significantly increased C_{max}, AUC, and $T_{1/2}$ of glimepiride by 23%, 22%, and 15%, respectively, and it decreased CL/f by 18%. The recovery of M1 and M2 from urine, however, did not change. The pharmacodynamic responses to glimepiride were nearly identical in normal subjects receiving propranolol and placebo. Pooled data from clinical trials in patients with NIDDM showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of beta-blockers. However, if beta-blockers are used, caution should be exercised and patients should be warned about the potential for hypoglycemia.

Concomitant administration of AMARYL® (glimepiride tablets) (4 mg once daily) did not alter the pharmacokinetic characteristics of R- and S-warfarin enantiomers following administration of a single dose (25 mg) of racemic warfarin to healthy subjects. No changes were observed in warfarin plasma protein binding. AMARYL® treatment did result in a slight, but statistically significant, decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and *maximum PT values during AMARYL® treatment were very small (3.3% and* 9.9%, respectively) and are unlikely to be clinically important.

The responses of serum glucose, insulin, C-peptide, and plasma glucagon to 2 mg AMARYL® were unaffected by coadministration of ramipril (an ACE inhibitor) 5 mg once daily in normal subjects. No hypoglycemic symptoms were reported. Pooled data from clinical trials in patients with NIDDM showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of ACE inhibitors.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. Potential interactions of glimepiride with other drugs metabolized by cytochrome P450 II C9 also include phenytoin, *diclofenac, ibuprofen, naproxen, and mefenamic acid.*

Although no specific interaction studies were performed, pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of calcium-channel blockers, estrogens, fibrates, NSAIDS, HMG CoA reductase inhibitors, sulfonamides, or thyroid hormone.

INDICATIONS AND USAGE

AMARYL® is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with noninsulin-dependent (Type II) diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet and exercise alone.

AMARYL® is also indicated for use in combination with insulin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic agent. Combined use of glimepiride and insulin may increase the potential for hypoglycemia.

In initiating treatment for noninsulin-dependent diabetes, diet and exercise should be emphasized as the primary form of treatment. Caloric restriction, weight loss, and exercise are essential in the obese diabetic patient. Proper dietary management and exercise alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. In addition to regular physical activity, 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 AMARYL® must be viewed by both the physician and patient as a treatment in addition to diet and exercise and not as a substitute for diet and exercise or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet and exercise alone may be transient, thus requiring only short-term administration of AMARYL®.

During maintenance programs, AMARYL® monotherapy should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations. Secondary failures to AMARYL® monotherapy can be treated with AMARYL®-insulin combination therapy.

In considering the use of AMARYL® in asymptomatic patients, it should be recognized that blood glucose control in NIDDM has not definitely been established to be effective in preventing the long-term cardiovascular and neural complications of diabetes. However, the Diabetes Control and Complications Trial (DCCT) demonstrated that control of HbA1c and glucose *was associated with a decrease in retinopathy, neuropathy, and nephropathy* for insulin-dependent diabetic (IDDM) patients.

CONTRAINDICATIONS

AMARYL® 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 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of AMARYL® (glimepiride tablets) 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. Patients with impaired renal function may be more sensitive to the glucose-lowering effect of AMARYL®. A starting dose of 1 mg once daily followed by appropriate dose titration is recommended in those patients. Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic 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 or other sympatholytic agents. 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 add insulin in combination with AMARYL® or even use insulin monotherapy. The effectiveness of any oral hypoglycemic drug, including AMARYL®, 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. Should secondary failure occur with AMARYL® monotherapy, AMARYL®-insulin combination therapy may be instituted. Combined use of glimepiride and insulin may increase the potential for hypoglycemia.

Information for Patients

Patients should be informed of the potential risks and advantages of AMARYL® and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of 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. The potential for primary and secondary failure should also be explained.

Laboratory Tests

Fasting blood glucose should be monitored periodically to determine therapeutic response. Glycosylated hemoglobin should also be monitored, usually every 3 to 6 months, to more precisely assess long-term glycemic control.

Drug Interactions

(See **CLINICAL PHARMACOLOGY, Drug Interactions.**)

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies in rats at doses of up to 5000 ppm in complete feed (approximately 340 times the maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation which was dose related and is thought to be the result of chronic pancreatic stimulation. The no-effect dose for adenoma formation in mice in this study was 320 ppm in complete feed, or 46-54 mg/kg body weight/day. This is about 35 times the maximum human recommended dose of 8 mg once daily based on surface area.

Glimepiride was non-mutagenic in a battery of *in vitro* and *in vivo* mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, mouse micronucleus test).

There was no effect of glimepiride on male mouse fertility in animals exposed up to 2500 mg/kg body weight (>1,700 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4000 mg/kg body weight (approx*imately 4,000 times the maximum recommended human dose based on* surface area).

Pregnancy

Teratogenic Effects. Pregnancy Category C. Glimepiride did not produce teratogenic effects in rats exposed orally up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately 60 times the maximum recommended human dose based on surface area). Glimepiride has been shown to be associated with intrauterine fetal death in rats when given in doses as low as 50 times the human dose based on surface area and in rabbits when given in doses as low as 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses inducing maternal hypoglycemia, has been similarly noted with other sulfonylureas, and is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride.

There are no adequate and well-controlled studies in pregnant women. On the basis of results from animal studies, AMARYL® (glimepiride tablets) should not be used during pregnancy. 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 glucose levels as close to normal as possible.

Nonteratogenic Effects. In some studies in rats, offspring of dams exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformities consisting of shortening, thickening, and bending of the *humerus during the postnatal period. Significant concentrations of* glimepiride were observed in the serum and breast milk of the dams as well as in the serum of the pups. These skeletal deformations were determined to be the result of nursing from mothers exposed to glimepiride.

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. Patients who are planning a pregnancy should consult their physician, and it is recommended that they change over to insulin for the entire course of pregnancy and lactation.

Nursing Mothers

In rat reproduction studies, significant concentrations of glimepiride were observed in the serum and breast milk of the dams, as well as in the serum of the pups. Although it is not known whether AMARYL® is excreted in human milk, other sulfonylureas are excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, and because of the effects on nursing animals, AMARYL® should be discontinued in nursing mothers. If AMARYL® is discontinued, and if diet and exercise alone are inadequate for controlling blood glucose, insulin therapy should be considered. (See above ***Pregnancy*, Nonteratogenic Effects.**)

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The incidence of hypoglycemia with AMARYL®, as documented by blood glucose values < 60 mg/dL, ranged from 0.9-1.7% in two large, well-controlled, 1-year studies. (See **WARNINGS** and **PRECAUTIONS.**)

AMARYL® has been evaluated for safety in 2,013 patients in US controlled trials, and in 1,551 patients in foreign controlled trials. More than 1,650 of these patients were treated for at least 1 year.

Adverse events, other than hypoglycemia, considered to be possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with AMARYL® are shown below.

Adverse Events Occurring in ≥ 1% AMARYL® Patients

	AMARYL®		Placebo	
	No.	%	No.	%
Total Treated	746	100	294	100
Dizziness	13	1.7	1	0.3
Asthenia	12	1.6	3	1.0
Headache	11	1.5	4	1.4
Nausea	8	1.1	0	0.0

Gastrointestinal Reactions

Vomiting, gastrointestinal pain, and diarrhea have been reported, but the incidence in placebo-controlled trials was less than 1%. Isolated transaminase elevations have been reported. Cholestatic jaundice has been reported to occur rarely with sulfonylureas.

Dermatologic Reactions

Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients. These *may be transient and may disappear despite continued use of AMARYL®; 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 reactions and disulfiram-like reactions have been reported with sulfonylureas; however, no cases have yet been reported with AMARYL® (glimepiride tablets). Cases of hyponatremia have been reported with glimepiride 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. The syndrome of inappropriate antidiuretic hormone (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 and/or increase release of ADH.

Other Reactions

Changes in accommodation and/or blurred vision may occur with the use of AMARYL®. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated. This condition is also seen in untreated diabetic patients, and may actually be reduced by treatment. In placebo-controlled trials of AMARYL®, the incidence of blurred vision was placebo, 0.7%, and AMARYL®, 0.4%.

Prescribing Information as of November 1996

Hoechst-Roussel Pharmaceuticals
Division of Hoechst Marion Roussel, Inc.
Kansas City, MO 64137 USA

US Patent 4,379,785

amab1196b

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2. American Diabetes Association. Position statement: implications of the Diabetes Control and Complications Trial. *Diabetes.* 1993;42:1555-1558.
3. Sonnenberg GE, Garg DC, Weidler DJ, et al. Short-term comparison of once- versus twice-daily administration of glimepiride in patients with non-insulin-dependent diabetes mellitus. *Ann Pharmacother.* 1997;31:671-676.

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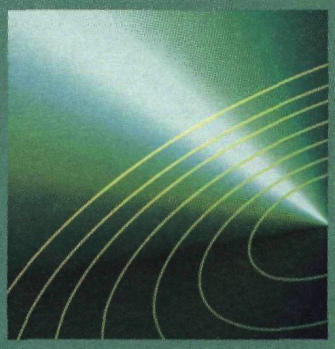

Wound Care Advances...1

Growth Factors: The Prime Agents of Wound Healing

Wound healing is a complex process, involving a series of well-orchestrated events set in motion by growth factors like platelet-derived growth factor (PDGF).

The emerging profile of growth factors and their role in wound healing

Wound healing is a series of processes including coagulation, inflammation, deposition and differentiation of the extracellular matrix, fibroplasia, epithelialization, contraction, and remodeling[1] resulting in regranulation and healing.

Currently, there is increasing interest in the role of growth factors, most broadly defined as any cytokine or combination of cytokines, peptides, or other substances that regulate the various processes of healing. Among the growth factors that have been identified are bFGF (basic fibroblast growth factor), EGF (epidermal growth factor), IL-1β (Interleukin-1β), TGF-α and β (transforming growth factor), and PDGF (platelet-derived growth factor).[1,2]

Pathophysiology of wounds – and the role of PDGF in healing

Platelet influx is the body's first response to an acute wound. Platelets are one of the most important agents in wound healing, releasing PDGF, which promotes a variety of activities in fibroblasts, smooth muscle cells, and capillary endothelial cells,[3] resulting in granulation.

Lately, growth factors have been the subject of research in patients with chronic wounds. As part of an ongoing commitment to advances in wound care, Ortho-McNeil will continue to provide you with the latest information in this emerging field.

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2. Bennett NT, Schultz GS. Growth factors and wound healing: biochemical properties of growth factors and their receptors. *Am J Surg.* 1993;165:728-737.
3. Ross R. Peptide regulatory factors: platelet derived growth factor. *Lancet.* 1989;I:1179-1182.

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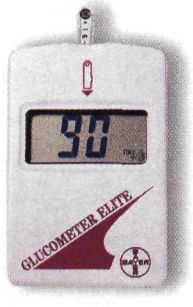

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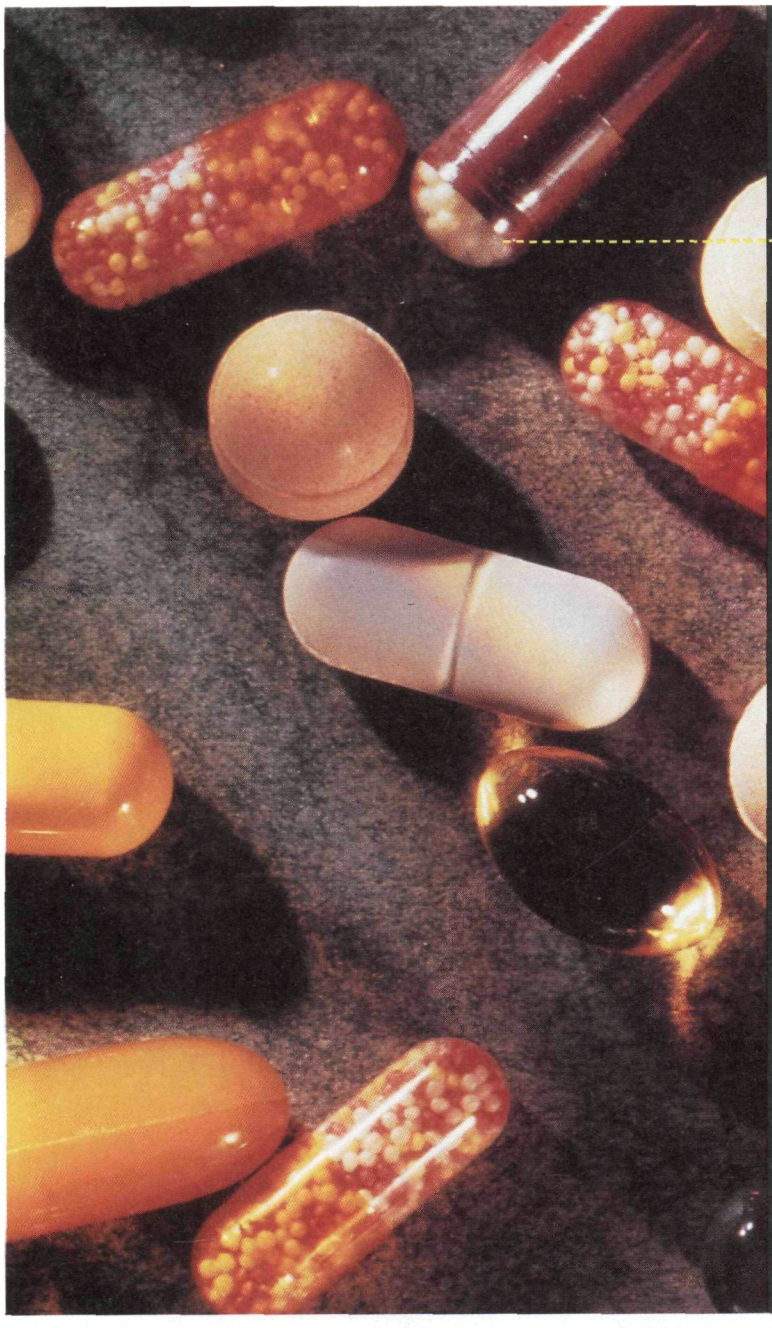

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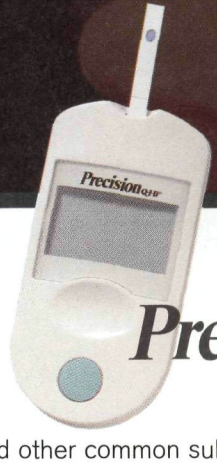

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