SEPTEMBER 1996 VOLUME 45 NUMBER 9

# diabetes



A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION®



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# How come the biggest breakthrough in diabetes happened 75 years ago?

*Starve or die.* That was the choice diabetic patients faced prior to 1922. By harnessing the power of insulin from animal sources, Banting and Best created a third option. Initially, insulin was a "miracle cure" that dramatically increased life expectancy. But as they lived longer, diabetics began to develop devastating sequelae. It became clear that insulin was not the cure. Yes, insulin was a miracle, but not a substitute for a healthy pancreas in achieving and regulating the delicate balance of insulin and glucose.

Unfortunately, while a lot more is known about diabetes today, nothing since has equaled the significance of the discovery of insulin seven decades ago. In contrast, the treatment options for other diseases—hypertension, for example—have multiplied both in number and in kind. *Why does it seem that the management and treatment of diabetes hasn't advanced much in comparison?*

Part of the answer is that diabetes has turned out to be more complex than ever dreamed of in the days of Banting and Best. Only now are researchers beginning to understand the etiology and the myriad of interacting factors that contribute to its development and progression. And, although we've come a long way in diminishing the morbidity and mortality of diabetes, there's still a long way to go.

## What *do* we know, what *don't* we know... and what are we doing about it?

By the 1920s, physicians had recognized the difference between the "acute" or "severe" diabetes found in younger people and the so-called "mild" or "fatty" diabetes usually seen in middle age. But it wasn't until 1960 that the radioimmunoassay (RIA) made it possible to measure insulin levels and to clearly differentiate patients who completely lacked insulin (Type I) from those who were both insulin deficient and insulin resistant (Type II).

*Measuring insulin levels led to the discovery that people with Type II diabetes didn't lack insulin. In fact, many had higher circulating insulin levels than nondiabetics.* Importantly, it was concluded that these patients might actually be resistant to the insulin produced by their own bodies. And for the last 30 years, scientists have been working to apply this knowledge.

*A significant gap seems to exist between what we know about diabetes and how we treat it.* Treatment options have not kept pace with our knowledge. For instance, despite the known differences between Type I and Type II diabetes, the most common approach to drug therapy for both diseases is oriented toward increasing insulin. As a result, clinicians tend to evaluate both types of patients only on the basis of glucose levels alone.

## What's new? Controversies, clues, causes.

The good news is that the unprecedented and encouraging level of interest in diabetes today is raising and answering some intriguing questions. *What chain of events culminates in the development of diabetes? Are there genes that can be isolated? Is there a therapeutic approach that's more physiologically appropriate? Should we think about diabetes differently than we have in the past? Will we be able to treat the disease differently? When is the best time to initiate treatment in order to best preserve health and potentially prevent cardiovascular and other complications?*

## Growing knowledge. Growing hope.

At Parke-Davis, we are gaining a greater understanding of diabetes. We believe that this understanding may help us devise ways to manage diabetes in a manner more consistent with the true nature of the disease. Our hope is to revolutionize the quality of life and long-term health of people with diabetes.

PARKE-DAVIS

**Source:** Krall, Levine, Barnett. The history of diabetes. In: Kahn CR, Weir GC, eds. *Joslin's Diabetes Mellitus.* 13th ed. Philadelphia, Pa:Lea & Febiger;1994:1–14.

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# diabetes

A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION®




**Mission Statement for *Diabetes***

***Diabetes* publishes original research about the physiology and pathophysiology of diabetes mellitus. Submitted manuscripts can report any aspect of laboratory, animal, or human research. Emphasis is on investigative reports focusing on areas such as the pathogenesis of diabetes and its complications, normal and pathologic pancreatic islet function and intermediary metabolism, pharmacological mechanisms of drug and hormone action, and biochemical and molecular aspects of normal and abnormal biological processes. Studies in the areas of diabetes education or the application of accepted therapeutic and diagnostic approaches to patients with diabetes mellitus are not published.**

Editorial correspondence and revised manuscripts should be sent by first-class mail to Julio V. Santiago, MD, Editor, *Diabetes* Editorial Office (Box 8218), Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO 63110; (314) 362-7809. All new manuscripts should be sent to the incoming editor: Gordon C. Weir, MD, *Diabetes* Editorial Office, Joslin Diabetes Center, One Joslin Place, Boston, MA 02215; (617) 735-1930.

*Diabetes* publishes only original material. When submitting a manuscript, authors must state in their transmittal letter that the material has not been published or submitted simultaneously to another journal. Accepted manuscripts incur a charge of $50 per printed page.

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* 324:424–428, 1991. "Instructions for Authors" containing specifications for manuscript preparation appears in the January and July issues.




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The mission of the American Diabetes Association is to prevent and cure diabetes and to improve the lives of all people affected by diabetes.

SEPTEMBER AUTHOR INDEX
(Volume 45, Number 9)

# 44th Annual Advanced

## Diabetes Care: Moving into the 21st Century

**American Diabetes Association's 44th Annual Advanced Postgraduate Course**

**January 17-19, 1997**

**New Orleans Hilton Riverside Hotel**

**New Orleans, Louisiana**

### FRIDAY, JANUARY 17

***General Session I: Research to Clinical Management: Insights for Diabetes Care***

New Techniques in the Diagnosis of Vascular Disease

Controversies in the Treatment of Hypertension

Oxidants and Antioxidant Therapy in the Prevention and Treatment of Diabetes Mellitus

Immune Markers and the Risk for Type I Diabetes

Insulin Action at the Cellular Level-Clinical Implications

***Concurrent General Session II-A: Endocrinology Issues***

Treatment Options for Osteoporosis

Pharmacologic Treatment of Impotence

Mineralocorticoids and Hypertension

Endocrinology of Prostate Disease

***Concurrent General Session II-B: Diabetes and the Older Adult***

Assessment of the Older Adult

Treatment and Management of Diabetes in the Older Adult

Psycho-Social Aspects of Diabetes in the Older Adult

Special Issues and Clinical Implications

### SATURDAY, JANUARY 18

***General Session III: Diabetes Care in the Future***

Defining Quality Care in a Managed Care Organization

Ensuring Quality Diabetes Care - Review of the ADA's Provider Recognition Program

Update on Medicare Diabetes Quality Improvement Project

# Postgraduate Course

New Pharmacologic Treatment Options for Diabetes

Update on Implantable Pumps

***Concurrent Workshops:***

Models of Health Care Delivery

Clinical Practice in the Age of Computers

New Nutrition Tools: Facilitating Lifestyle Change, The First Steps in Diabetes Meal Planning and Single Topic Resources

Insulin Pumps: What's New in Patient Management?

Behavior Modification: Maintaining Patient/ Provider Agreement

Treatment Issues in Children and Adolescents

Intensifying Therapy for Type II Patients

## SUNDAY, JANUARY 19

***General Session IV: Obesity - What's New in Treatment and Management?***

Physiology of Body Weight Regulation

Effective Communication Strategies for Implementing Lifestyle Behavior Change

Pharmacologic and Non-Pharmacologic Treatments of Obesity

Join us in New Orleans for innovative sessions of interest to all health-care professionals in the field of diabetes. This year's program highlights new information on topics and issues related to: diabetes care now and in the future; endocrinology issues; diabetes and the older adult; and treatment and management of obesity in patients with diabetes. Lecture presentations and interactive workshops promise to provide a rewarding educational opportunity for attendees.

Christened on the banks of a great river, New Orleans celebrates its heritage year 'round. The fun ranges from its fanciful street parades and formal balls of Mardi Gras to the jubilant Jazz and Heritage Festival, from the Cajun restaurants to victorian mansions and plantation homes.

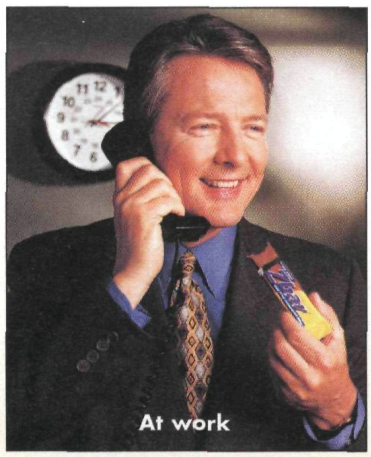
Through its years of growth, New Orleans has not forgotten its European legacy, nor abandoned the flavor of the old South. The French Quarter retains its charm, the ante-bellum splendor still lingers in the Garden District and the famous Cabildo, where Thomas Jefferson signed the Louisiana Purchase, still overlooks the Jackson Square.

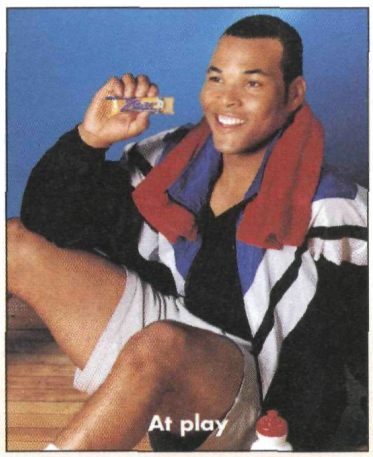
44th Annual Advanced Postgraduate Course
NEW ORLEANS

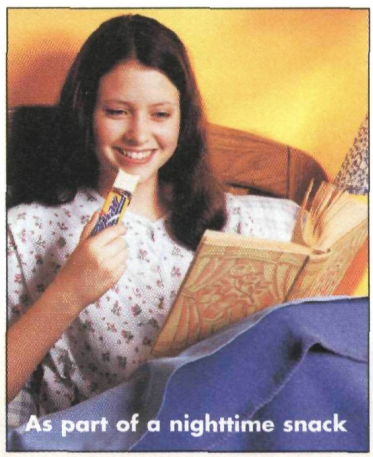
**For more information contact:**
**American Diabetes Association**
**Meeting Services Department**
**1660 Duke Street**
**Alexandria, VA 22314-3447 USA**
**Phone: 703/549-1500, ext. 2453**
**Fax: 703/683-1351**
**E-mail: meetings@diabetes.org**


American Diabetes Association.

# Reduce the risk
## of hypoglycemic episodes

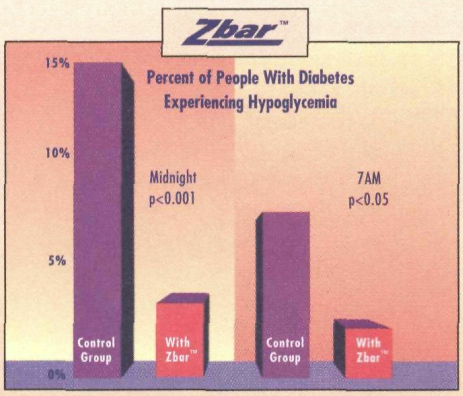



### DCCT Study — Changing diabetes management

Findings of the Diabetes Control and Complications Trial showed that lowering blood sugar levels using intensive insulin therapy delays the onset and progression of ophthalmological, renal, and neurological diseases caused by diabetes. However, there is one problem inherent with this therapy— **the increased incidence of hypoglycemic episodes.**




### *Zbar*™— Reducing the risk of hypoglycemic episodes...up to 9 hours

***Zbar***™ is a new medical food formulated with *uncooked cornstarch*. Clinical research demonstrated that including ***Zbar***™ as a snack, in a total diabetes dietary management program, regulated blood glucose levels for an extended period of time. In addition, studies showed that the incidence of hypoglycemic episodes was reduced (78% at midnight; 74% at 7 a.m.).*

### *Zbar*™— Making compliance easier

***Zbar***™ is available in three great tasting flavors—making it easier for your patients to comply with your diabetes dietary management regimen.


Patent Pending

## Reduce the incidence of hypoglycemic episodes — recommend Zbar™

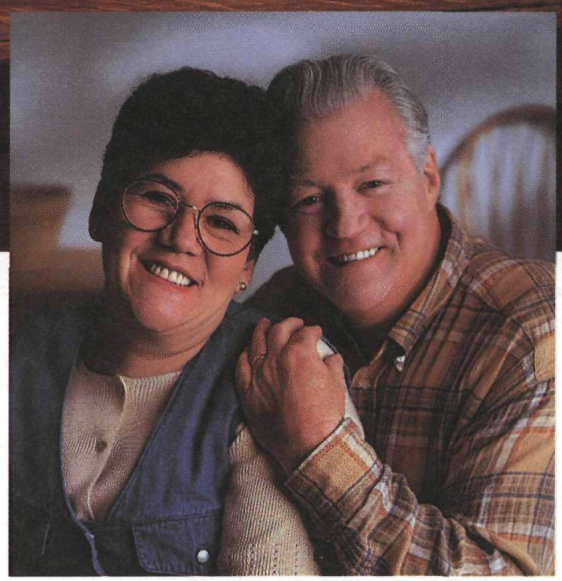
For product samples & patient education materials call **(800) 735-2315.**

***Zbar***™ is a medical food developed for use under medical supervision.

* References: Kaufman FR; Halvorson M; Kaufman ND. Evaluation of a snack bar containing uncooked cornstarch in normal controls and subjects with diabetes (Abstract). *Diabetes 45 (Suppl. 2): 56A, 1996.*

Now that they have diabetes, they know how crucial diet and exercise are.

# Since it's hard to change lifestyle, their first diabetic agent should be easy.



Choose it for **control.**

Choose it for **convenience.**

Choose it for improved patient **quality of life.**[1]

**When diet alone fails in NIDDM*...**

ONCE DAILY **GlucotrolXL®**
(glipizide) extended release
Tablets 5 mg and 10 mg GITS†

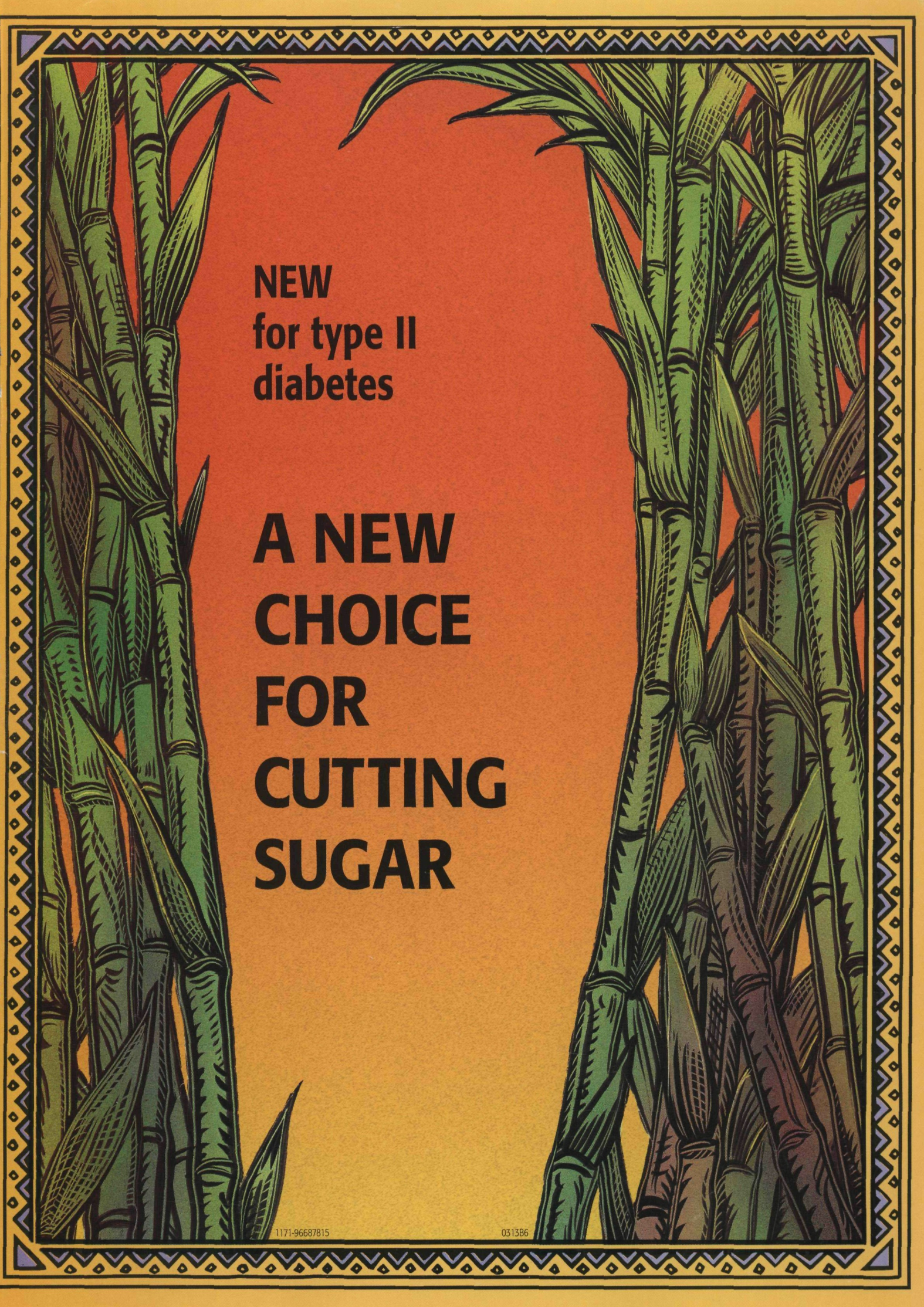
DIET EXERCISE

* Non–insulin-dependent diabetes mellitus.
† Gastrointestinal therapeutic system.

**As with all sulfonylureas, hypoglycemia may occur.**

*Please see brief summary of prescribing information on adjacent page.*

**Reference: 1.** Testa MA, Simonson DC. Beneficial effects of glipizide GITS on glycemic control, quality of life and symptom distress in NIDDM. *Diabetes.* May 1996;45(suppl 2):123A. Abstract 450.


NEW
for type II
diabetes
A NEW
CHOICE
FOR
CUTTING
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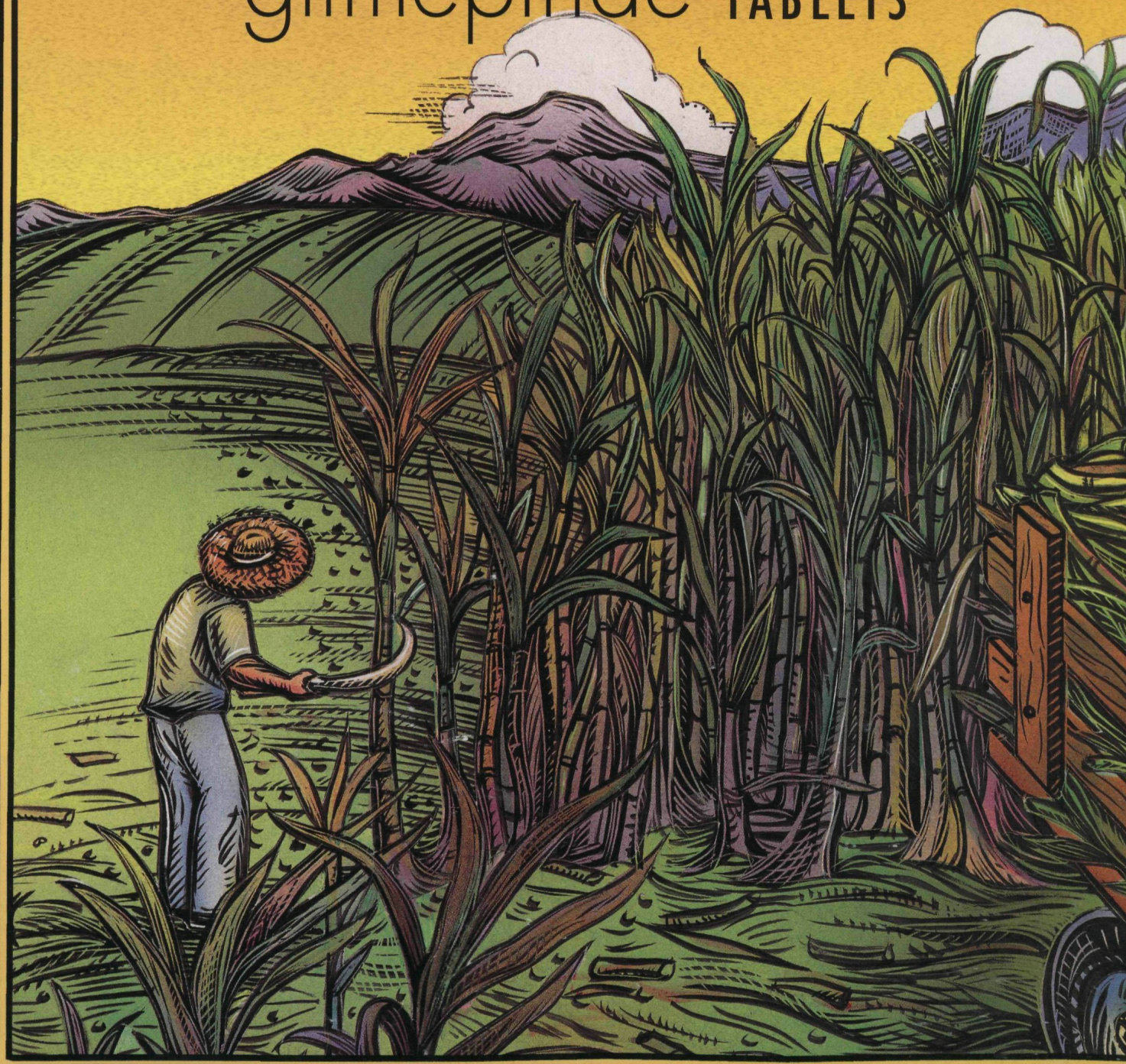
INTRODUCING a new adjunct to diet and exercise

**NEW ONCE-A-DAY**

# Amaryl®

## glimepiride TABLETS



# INSULIN-SPARING GLUCOSE CONTROL

- **A new sulfonylurea**
- **Amaryl binds to a different part of the sulfonylurea receptor complex***[1,2]—the clinical relevance of this mechanism has not been established
- **Amaryl provides sustained blood glucose control** even in patients with higher levels of $HbA_{1c}$ (glycosylated hemoglobin)[3]
- **Amaryl is insulin sparing**—controls glucose without clinically meaningful increases in fasting insulin
- **Amaryl is indicated** for both monotherapy and second-line combination use with insulin†
- **Favorable safety profile**[3]—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 glucose values <60 mg/dL
- **Proven 24-hour control** with once-daily dosing

*Data derived from preclinical animal model. The mechanism by which sulfonylureas lower blood glucose during long-term use has not been clearly established.

†Combined use of Amaryl and insulin may increase the potential for hypoglycemia.

Please see brief summary of Prescribing Information on last page of this advertisement.

1171-96687815 0313B6

# Amaryl®
glimepiride TABLETS

**1, 2, and 4 mg**
**Brief Summary**
**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.

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.

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.

**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.**

**PRECAUTIONS**
***General***
Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. 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 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. 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.

***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 (approximately 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 should not be used during pregnancy. 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. 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. 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%.

**OVERDOSAGE**
Overdosage 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, because hypoglycemia may recur after apparent clinical recovery.

**DOSAGE AND ADMINISTRATION**
There is no fixed dosage regimen for the management of diabetes mellitus with AMARYL or any other hypoglycemic agent.

***Usual Starting Dose***
The usual starting dose of AMARYL as initial therapy is 1-2 mg once daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1 mg once daily, and should be titrated carefully. (See **PRECAUTIONS** Section for patients at increased risk).

No exact dosage relationship exists between AMARYL and the other oral hypoglycemic agents. The maximum starting dose of AMARYL should be no more than 2 mg.

Failure to follow an appropriate dosage regimen may precipitate hypoglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy.

***Usual Maintenance Dose***
The usual maintenance dose is 1 to 4 mg once daily. The maximum recommended dose is 8 mg once daily. After reaching a dose of 2 mg, dosage increases should be made in increments of no more than 2 mg at 1-2 week intervals based upon the patient's blood glucose response. Long-term efficacy should be monitored by measurement of HbA1c levels, for example, every 3 to 6 months.

***AMARYL®-Insulin Combination Therapy***
Combination therapy with AMARYL and insulin may be used in secondary failure patients. The fasting glucose level for instituting combination therapy is in the range of >150 mg/dL in plasma or serum depending on the patient. The recommended AMARYL dose is 8 mg once daily administered with the first main meal. After starting with low-dose insulin, upward adjustments of insulin can be done approximately weekly as guided by frequent measurements of fasting blood glucose. Once stable, combination-therapy patients should monitor their capillary blood glucose on an ongoing basis, preferably daily. Periodic adjustments of insulin may also be necessary during maintenance as guided by glucose and HbA1c levels.

***Specific Patient Populations***
AMARYL is not recommended for use in pregnancy, nursing mothers, or children. In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions (See **PRECAUTIONS**, ***General***).

HOECHST-ROUSSEL
Pharmaceuticals Incorporated
Somerville, NJ 08876-1258
REG TM HOECHST AG

922100 - 10/95

**References: 1.** Kramer W, Müller G, Girbig F, et al. Differential interaction of glimepiride and glibenclamide with the β-cell sulfonylurea receptor: II. photoaffinity labeling of a 65 kDa protein by [$^3$H]glimepiride. *Biochim Biophys Acta.* 1994;1191:278-290. **2.** Müller G, Hartz D, Pünter J, Ökonomopulos R, Kramer W. Differential interaction of glimepiride and glibenclamide with the β-cell sulfonylurea receptor: I. binding characteristics. *Biochim Biophys Acta.* 1994; 1191:267-277. **3.** Data on file, Hoechst Marion Roussel.

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