

diabetes

ABSTRACT FORM FOR 57th SCIENTIFIC SESSIONS INCLUDED; SUBMISSION DEADLINE IS JANUARY 6, 1997

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.

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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.



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 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.

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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.

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January 17-19, 1997
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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

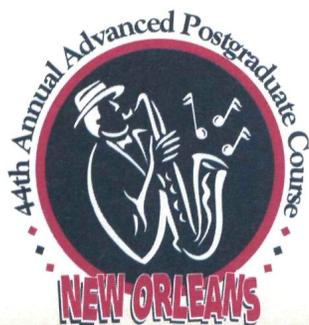
**General Session IV: Obesity - What's New in
Treatment and Management?**

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.

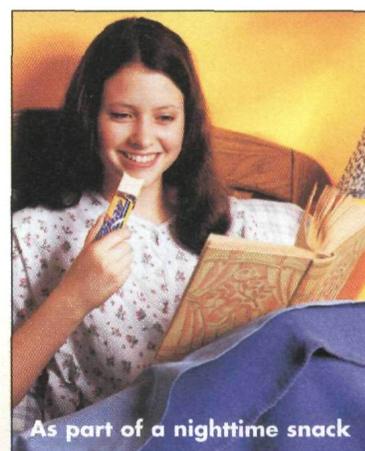
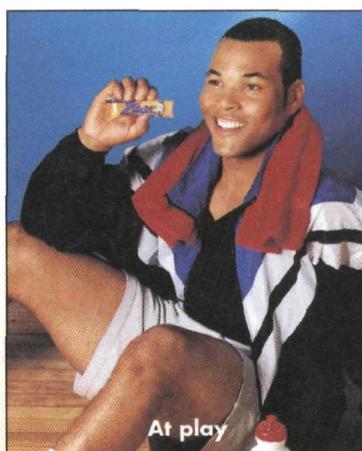
Through its years of growth, New Orleans has not forgotten its European legacy, nor abandoned the flavor of the old South. The French Quarter retains its charm, the ante-bellum splendor still lingers in the Garden District and the famous Cabildo, where Thomas Jefferson signed the Louisiana Purchase,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



**For more information contact:
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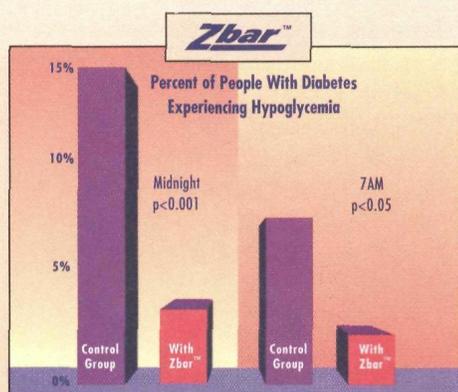


Reduce the risk of hypoglycemic episodes



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.).*

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



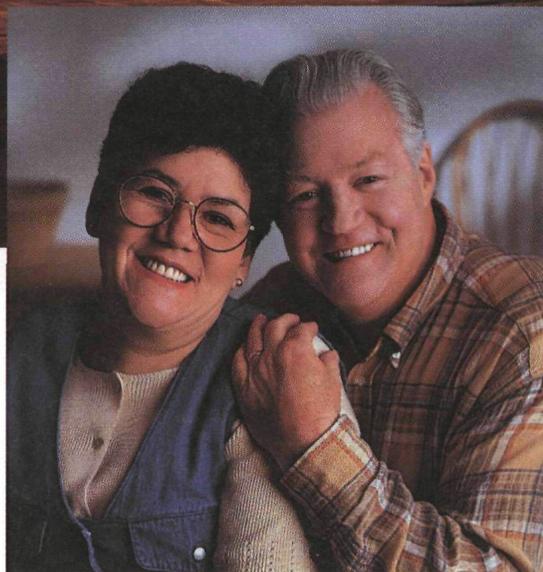
Reduce the incidence of hypoglycemic episodes — recommend **Zbar™**
 For product samples & patient education materials call (800) 735-2315.

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.

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Tablets 5 mg and 10 mg GITS[†]

*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.

GLUCOTROL XL* (glipizide) Extended Release Tablets For Oral Use

Brief Summary of Prescribing Information

INDICATIONS AND USAGE: GLUCOTROL XL 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.

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

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.

As with any other non-deformable material, caution should be used when administering GLUCOTROL XL Extended Release Tablets in patients with preexisting severe gastrointestinal narrowing (pathologic or atrophic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of another drug in this non-deformable sustained release formulation.

PRECAUTIONS: Renal and Hepatic Disease: The pharmacokinetics and/or pharmacodynamics of glipizide may be affected in patients with impaired renal or hepatic function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted.

GI Disease: Markedly reduced GI retention times of the GLUCOTROL XL Extended Release Tablets may influence the pharmacokinetic profile and hence the clinical efficacy of the drug.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Renal or hepatic insufficiency may affect the disposition of glipizide 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 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 glipizide and administer insulin.

Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

Laboratory Tests: Blood and urine glucose should be monitored periodically. Measurement of hemoglobin A_{1c} may be useful.

Information for Patients: Patients should be informed that GLUCOTROL XL Extended Release Tablets should be swallowed whole. Patients should not chew, divide or crush tablets. Patients should not be concerned if they occasionally notice in their stool something that looks like a tablet. In the GLUCOTROL XL Extended Release Tablet, the medication is contained within a nonabsorbable shell that has been specially designed to slowly release the drug so the body can absorb it. When this process is completed, the empty tablet is eliminated from the body. Patients should be informed of the potential risks and advantages of GLUCOTROL XL 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 also should 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. *In vitro* binding studies with human serum proteins indicate that glipizide 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 glipizide with these drugs.

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

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. The effect of concomitant administration of Diflucan® (fluconazole) and Glucotrol® has been demonstrated in a placebo-controlled crossover study in normal volunteers. All subjects received Glucotrol alone and following treatment with 100 mg of Diflucan® as a single daily oral dose for 7 days. The mean percentage increase in the Glucotrol AUC after fluconazole administration was 55.9% (range: 35 to 81%).

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. 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 glipizide. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well controlled studies in pregnant women. Glipizide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 glipizide 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 glipizide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. A decision should be made whether to discontinue nursing or to discontinue the drug, 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.

Geriatric Use: Of the total number of patients in clinical studies of GLUCOTROL XL*, 33 percent were 65 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some individuals cannot be ruled out. Approximately 1-2 days longer were required to reach steady-state in the elderly. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS: In U.S. controlled studies the frequency of serious adverse experiences reported was very low and causal relationship has not been established.

The 580 patients from 31 to 87 years of age who received GLUCOTROL XL Extended Release Tablets in doses from 5 mg to 60 mg in both controlled and open trials were included in the evaluation of adverse experiences. All adverse experiences reported were tabulated independently of their possible causal relation to medication.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

In double-blind, placebo-controlled studies the adverse experiences reported with an incidence of 3% or more in GLUCOTROL XL-treated patients (N=278) and placebo-treated patients (N=69) respectively, include: Asthenia - 10.1% and 13.0%; Headache - 8.6% and 8.7%; Dizziness - 6.8% and 5.8%; Nervousness - 3.6% and 2.9%; Tremor - 3.6% and 0.0%; Diarrhea - 5.4% and 0.0%; Flatulence - 3.2% and 1.4%.

The following adverse experiences occurred with an incidence of less than 3% in GLUCOTROL XL-treated patients: Body as a whole - pain; Nervous system - insomnia, paresthesia, anxiety, depression and hyposthesia; Gastrointestinal - nausea, dyspepsia, constipation and vomiting; Metabolic - hypoglycemia; Musculoskeletal - arthralgia, leg cramps and myalgia; Cardiovascular - syncope; Skin - sweating and pruritus; Respiratory - rhinitis; Special senses - blurred vision; Urogenital - polyuria.

Other adverse experiences occurred with an incidence of less than 1% in GLUCOTROL XL-treated patients: Body as a whole - chills; Nervous system - hypertension, confusion, vertigo, somnolence, gait abnormality and decreased libido; Gastrointestinal - anorexia and trace blood in stool; Metabolic - thirst and edema; Cardiovascular - arrhythmia, migraine, flushing and hypertension; Skin - rash and urticaria; Respiratory - pharyngitis and dyspnea; Special senses - pain in the eye, conjunctivitis and retinal hemorrhage; Urogenital - dysuria. There have been rare reports of gastrointestinal irritation and gastrointestinal bleeding with use of another drug in this non-deformable sustained release formulation, although causal relationship to the drug is uncertain.

The following are adverse experiences reported with immediate release glipizide and other sulfonylureas, but have not been observed with GLUCOTROL XL:

Hematology: 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, glipizide pretreatment did not cause an accumulation of acetaldehyde after ethanol administration. Clinical experience to date has shown that glipizide has an extremely low incidence of disulfiram-like alcohol reactions.

Endocrine Reactions: Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with glipizide and other sulfonylureas.

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 neurologic impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given 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 glipizide from plasma may be prolonged in persons with liver disease. Because of the extensive protein binding of 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 XL Extended Release Tablet or any other hypoglycemic agent.

In general, GLUCOTROL XL should be given with breakfast.

Recommended Dosing: The recommended starting dose of GLUCOTROL XL is 5 mg per day, given with breakfast. The recommended dose for geriatric patients is also 5 mg per day.

Dosage adjustment should be based on laboratory measures of glycemic control. While fasting blood glucose levels generally reach steady-state following initiation or change in GLUCOTROL XL dosage, a single fasting glucose determination may not accurately reflect the response to therapy. In most cases, hemoglobin A_{1c} level measured at three month intervals is the preferred means of monitoring response to therapy.

Hemoglobin A_{1c} should be measured as GLUCOTROL XL therapy is initiated at the 5 mg dose and repeated approximately three months later. If the result of this test suggests that glycemic control over the preceding three months was inadequate, the GLUCOTROL XL dose may be increased to 10 mg. Subsequent dosage adjustments should be made on the basis of hemoglobin A_{1c} levels measured at three month intervals. If no improvement is seen after three months of therapy with a higher dose, the previous dose should be resumed. Decisions which utilize fasting blood glucose to adjust GLUCOTROL XL therapy should be based on at least two or more similar, consecutive values obtained seven days or more after the previous dose adjustment.

Most patients will be controlled with 5 mg or 10 mg taken once daily. However, some patients may require up to the maximum recommended daily dose of 20 mg. While the glycemic control of selected patients may improve with doses which exceed 10 mg, clinical studies conducted to date have not demonstrated an additional group average reduction of hemoglobin A_{1c} beyond what was achieved with the 10 mg dose.

More detailed information available on request.

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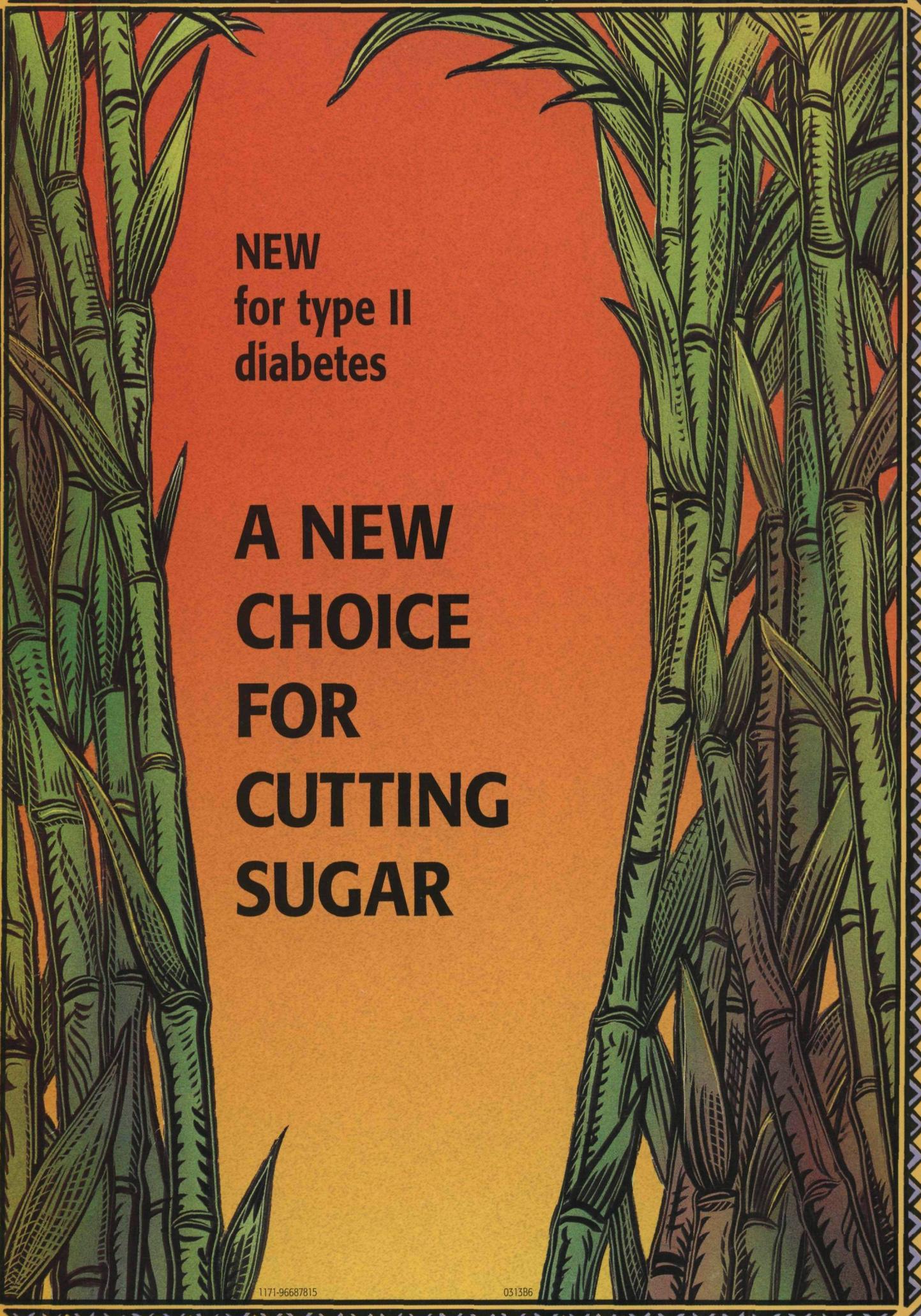
<http://www.ada.judds.com>

The American Diabetes Association has introduced new World Wide Web services for members and subscribers. The publications home page offers:

- Tables of contents and a searchable database of abstracts from the current and back issues of *Diabetes* and *Diabetes Care*.
- Full text of *Clinical Practice Recommendations 1996*, the

Association's annual compendium of position and consensus statements.

- Tables of contents and selected articles from *Diabetes Spectrum* and *Diabetes Forecast*.
- Information about and online ordering for books and other resources for health professionals and people with diabetes.
- Information about and online ordering for membership in the Professional Section of the American Diabetes Association.
- Links to other diabetes sites on the Internet, including newsgroups and World Wide Web pages.
- A professional-to-professional forum for discussing articles in Association publications and other issues in diabetes research and treatment. (This service is available only to Professional Section members of the American Diabetes Association.)

A stylized illustration of sugarcane stalks in shades of green and yellow, set against a background that transitions from red at the top to yellow at the bottom. The stalks are detailed with leaves and sheaths. The entire composition is framed by a decorative border with a repeating geometric pattern.

NEW
for type II
diabetes

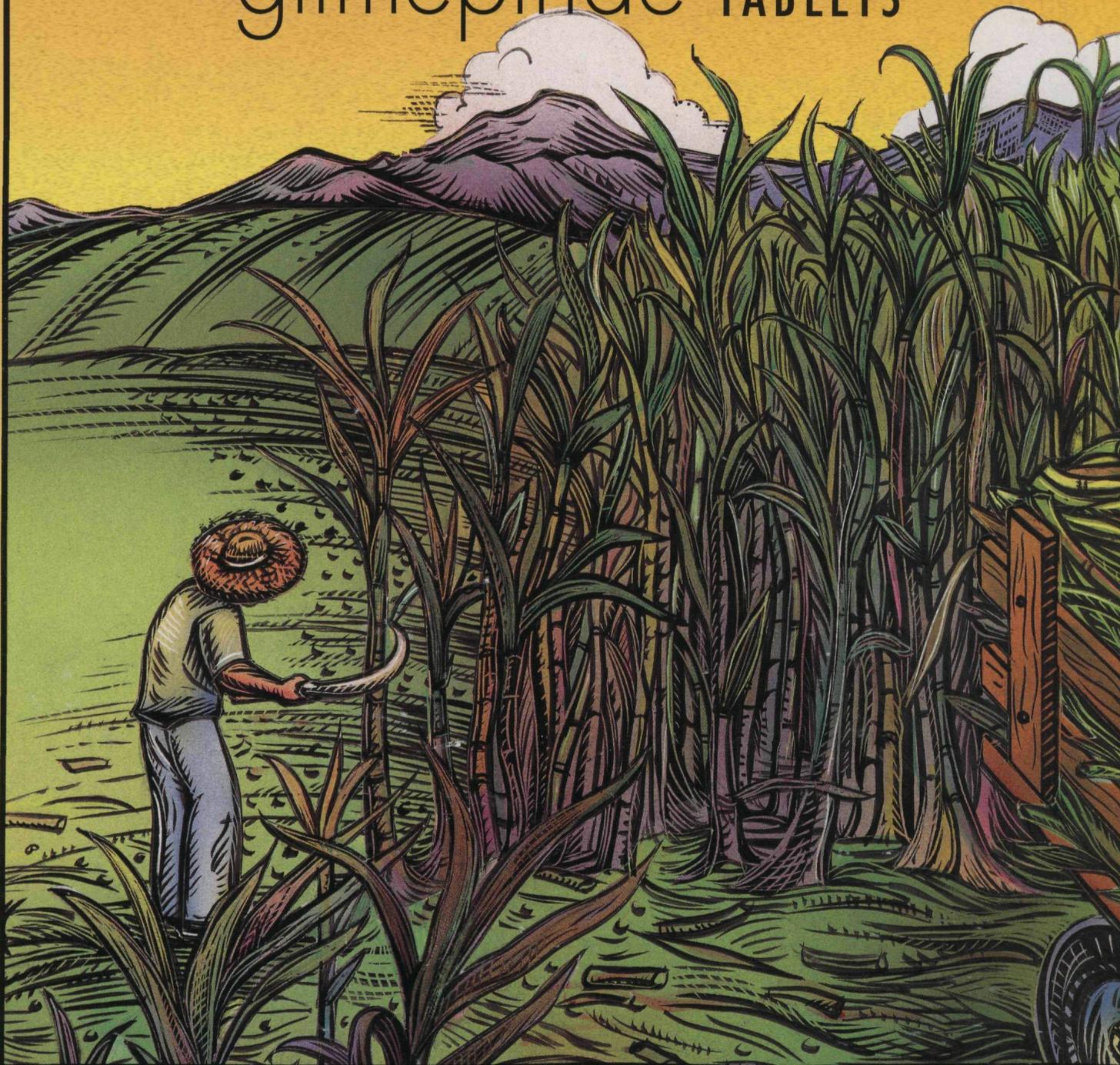
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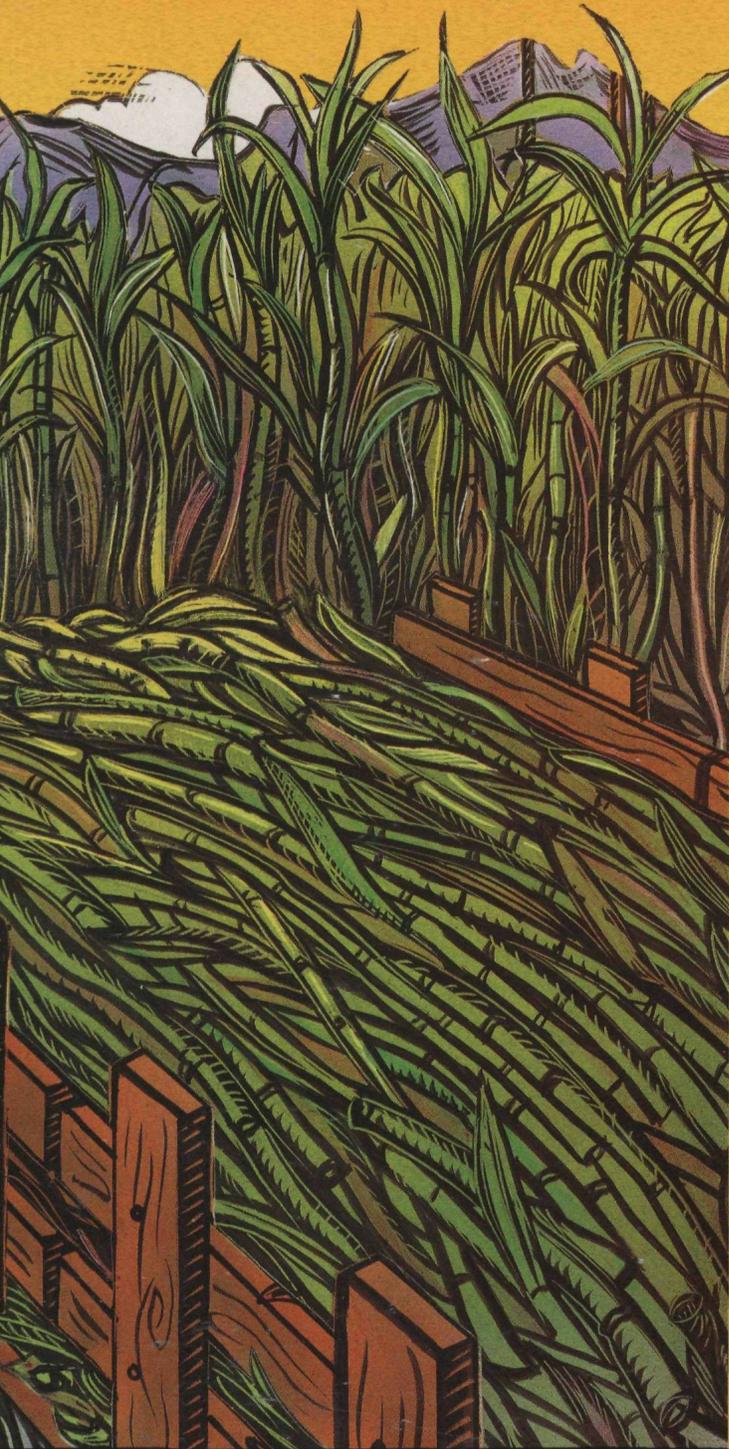
NEW O N C E - A - D A Y

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 profile³**—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.

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. Dehydrated 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 clinical 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**).



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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, Ökonomopoulos 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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