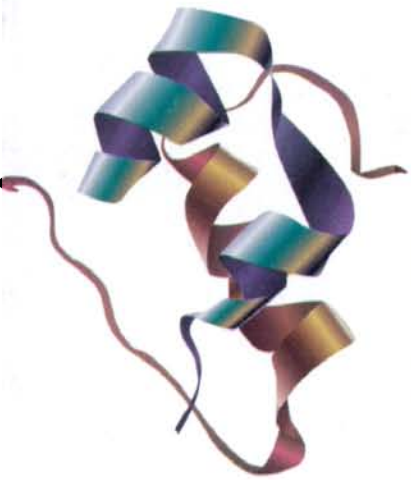
MAY 1997 VOLUME 46 NUMBER 5

diabetes

A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION®
www.diabetes.org/diabetes



DIAEAZ 46(5) 735–927 (1997)
ISSN 0012-1797

►*Table of contents continues on page iii.*

The Simple Truth About Blood Glucose Monitoring

In the real world,

your patients need to get a true blood glucose value,

not just a number

With an advanced biosensor system, your patients can achieve clinical accuracy in their everyday monitoring.

The truth is, all blood glucose monitors are accurate under laboratory testing conditions. But in the real world, many factors can alter readings and affect accuracy. Which means your patients may not really be achieving tight blood glucose control. And they may not even know it.

Readings can be affected by everyday things such as dried blood and dirt collecting on the optical window, and bright light overwhelming the photometric system. Humidity or a simple touch can degrade test strip reagents. In addition, an inadequate blood sample can produce a significantly lowered reading. More importantly, test accuracy may be compromised by interactions with drugs, vitamins and other substances present in the body.

But with the advanced biosensor technology of the Precision Q•I•D® Blood Glucose System, your patients can achieve accurate blood glucose values while testing at home by eliminating common test errors.* The Precision Q•I•D Monitor requires no cleaning, and its sensors are unaffected by bright light. Each MICROFLO™ test strip reagent pad is protected from degradation caused by humidity** or touching.

It requires only a 5µl blood sample. If needed, a second drop of blood may be added to the test strip to accurately complete a test. In addition, the unique MICROFLO™ test strips make Precision Q•I•D the only system that automatically compensates for the effects of drugs, vitamins and other substances.*

The Precision Q•I•D Blood Glucose System, with individually foil wrapped test strips, provides true, accurate readings in the real world, not just in the laboratory. And when it comes to your patients and their blood glucose control, that can make all the difference in the world.

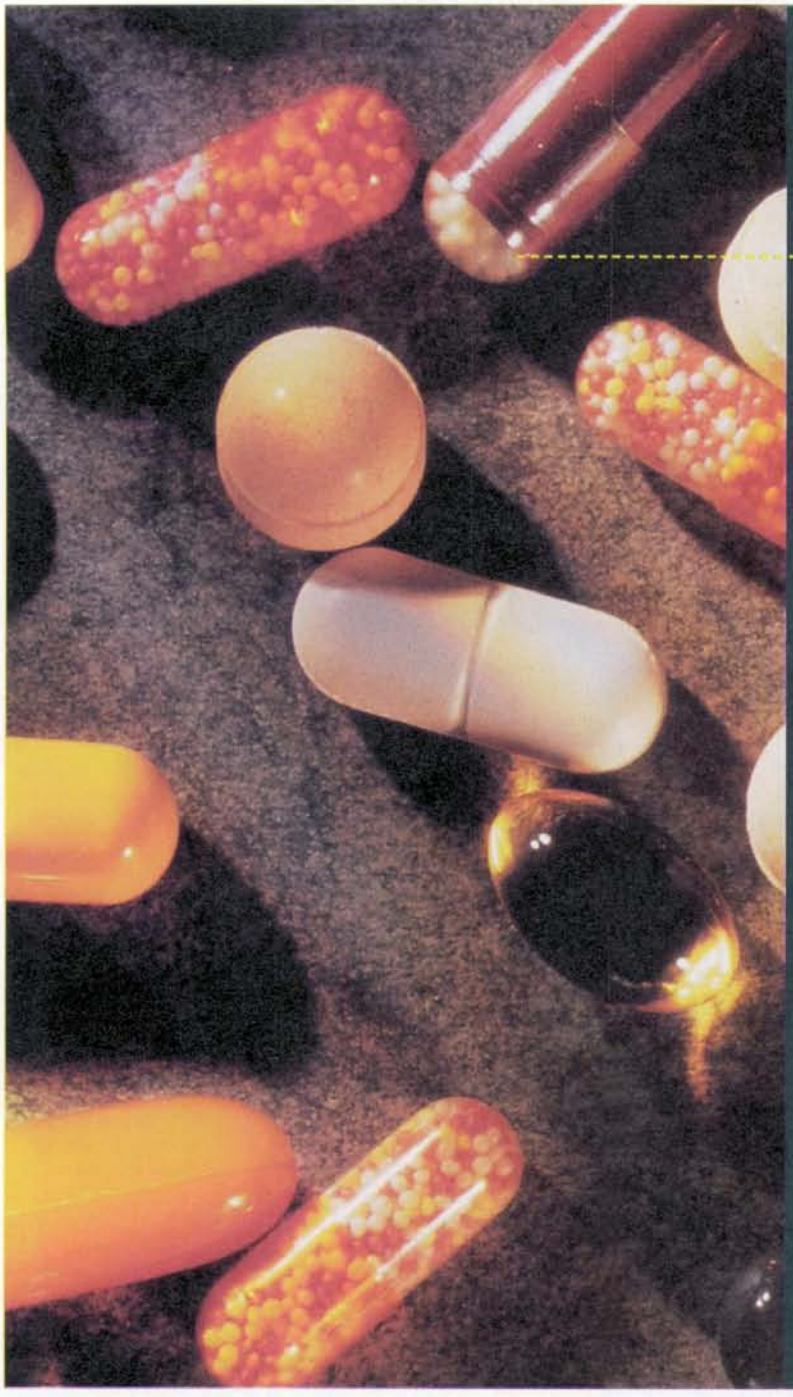
For detailed information on advanced biosensor technology, the Precision Q•I•D System, and the importance of real accuracy in the real world contact us at

1-800-527-3339.

MEDISENSE®

An Abbott Laboratories Company

*Data on file.
**Foil wrapped test strips



IN THE REAL WORLD, **DRUGS** CAN INTERFERE WITH YOUR PATIENTS KNOWING THEIR TRUE BLOOD GLUCOSE VALUE.

THAT'S WHY THERE'S

Precision Q·I·D™

Everyday substances like drugs and vitamins can cause inaccurate blood glucose readings. Which means your patients may not be getting the true blood glucose values they need for tight control. And they may not even know it.

Precision Q·I·D™ **System**

The ***Precision*** Q·I·D™ System is the only blood glucose monitoring system that automatically compensates for the interactions of drugs, vitamins and other common substances. Your patients get accurate blood glucose values in everyday testing. The ***Precision*** Q·I·D™ System is clinically proven to eliminate common test errors such as ambient light, dried blood and dirt, and humidity.*

Precision Q·I·D™ for clinical accuracy in everyday monitoring.

Real Accuracy for the Real World

MEDISENSE®
An Abbott Laboratories Company

For more information call 1-800-527-3339.

*Individually foil-wrapped test strips.

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.**

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.

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 $60 per printed page.

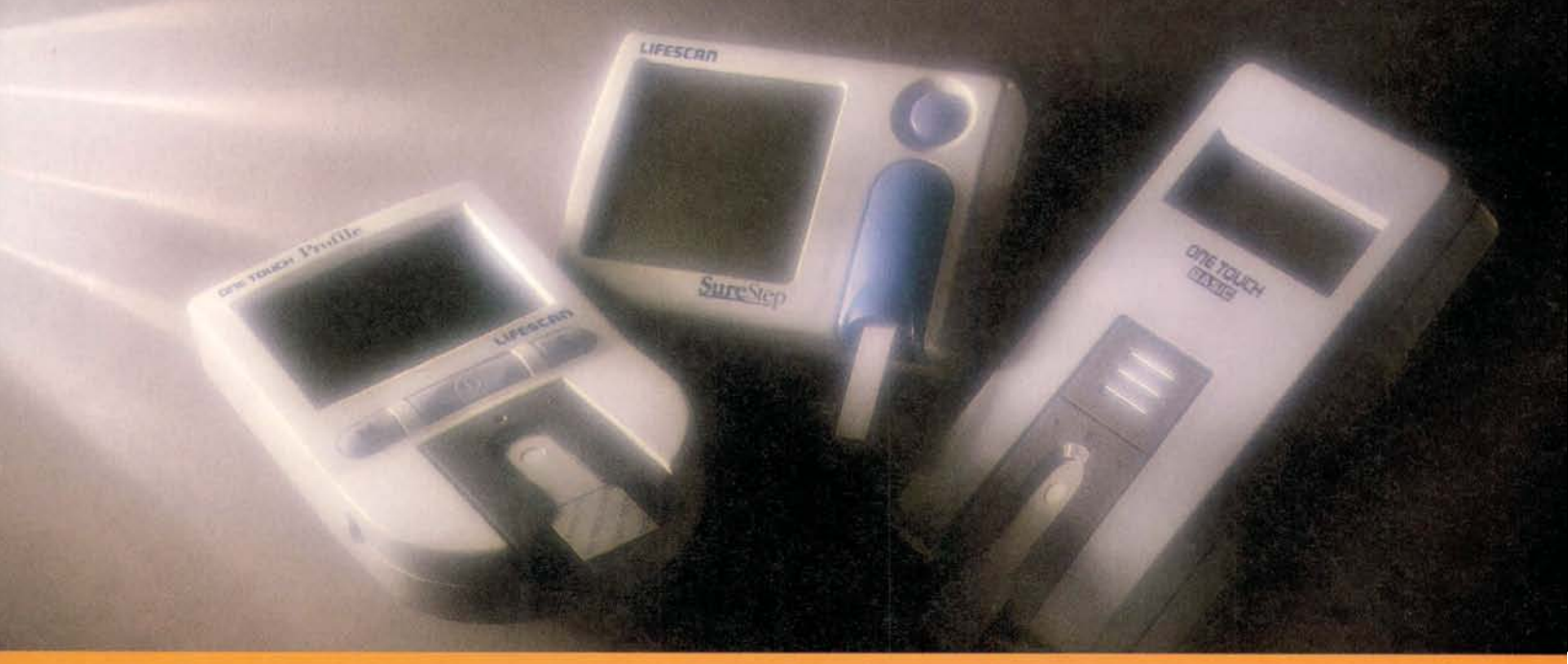
Manuscripts should be prepared in accordance with the requirements specified in the document "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," *New England Jonrnal of Medicine* 324:424–428, 1991. "Instructions for Authors" containing specifications for manuscript preparation appears in the January and July issues of *Diabetes*.

Diabetes (ISSN 0012-1797) is published monthly by the American Diabetes Association, Inc., 1660 Duke Street, Alexandria, Virginia 22314. Professional membership dues include $75 designated for *Diabetes*. Individual subscription rates are $150 in the U.S., Canada, and Mexico (for Canada add 7% GST) and $210 for all other countries. Institutional subscription rates are $240 in the U.S., Canada, and Mexico (for Canada add 7% GST) and $300 in all other countries. Single issues are $18.00 in the U.S., Canada, and Mexico (for Canada add 7% GST) and $21.50 for all other countries. Periodicals postage paid at Alexandria, Virginia 22314, and at additional mailing offices. POSTMASTER: Send change of address to *Diabetes*, American Diabetes Association, Journal Subscriptions, 1660 Duke St., Alexandria, VA 22314.

Diabetes is listed in *Science Citation Index*, *MEDLARS*, *Index Medicus*, *EMBASE*, and *Current Contents* (*Basic Science* and *Clinical Medicine*) databases and *Automatic Subject Citation Alert*. *Diabetes* is available online on *BRS Colleague* (for more information, call 800-955-0906) and in machine-readable format from University Microfilms International. *Diabetes* is printed on acid-free paper starting with Vol. 37, 1988.

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

MAY AUTHOR INDEX (Volume 46, Number 5)



We take diabetes very personally.

That's why LifeScan makes three distinctly different blood glucose meters. All easy to learn. All easy to use. All of which makes your job of teaching patients the fundamentals of monitoring and diabetes management a whole lot easier. Something your patients will thank you for, personally.

For meters that meet your patients' needs, look to LifeScan—makers of the ONE TOUCH® family of products, the brand recommended by more healthcare professionals than any other.

ONE TOUCH® Profile™

Complete Diabetes Tracking System

It's great for your patients who use insulin, or who want to actively manage their diabetes.

SureStep®

Blood Glucose Monitoring System

A reassuring choice for patients who have difficulty testing and who want to be sure at every step.

ONE TOUCH® BASIC®

Blood Glucose Monitoring System

It's ideal for patients who want a simple, accurate test.

For diabetes and life.

LIFESCAN INC.

a Johnson & Johnson company

"We all walk to feel healthier. But how we each manage our diabetes is based on personal needs. We're glad LifeScan makes meters that recognize our differences."

American Diabetes Association's 57th Scientific Sessions

Join your colleagues in Boston for the American Diabetes Association's 57th Scientific Sessions, June 21-24, 1997.

WHAT'S NEW FOR THE 1997 SCIENTIFIC SESSIONS?

THEMES

The Scientific Sessions program has been expanded to include seven theme areas focusing on the latest in basic and clinical research:

- Cell & Molecular Biology of the Islet
- Complications
- Genetics & Epidemiology
- Health Care Delivery and Education
- Immunology, Autoimmunity & Transplantation
- Insulin Action, the Fat Cell & Vesicular Trafficking
- Nutrition/Obesity

30 Symposia
11 Current Issues
19 Workshops
5 Meet-The-Professor
35 Oral Sessions
3 Full Days of Poster Sessions

POSTER PRESENTATIONS

This year, for the first time, all abstracts selected for poster presentation will be available for viewing throughout the Scientific Sessions. You will be able to visit the posters anytime during the Exhibit Hall's open hours.

WORKSHOPS

Seven interactive workshops will be presented multiple times for a total of 19 workshops. Advance registration is not necessary. Tickets will be available on a first-come, first-served basis on the day of the workshop.

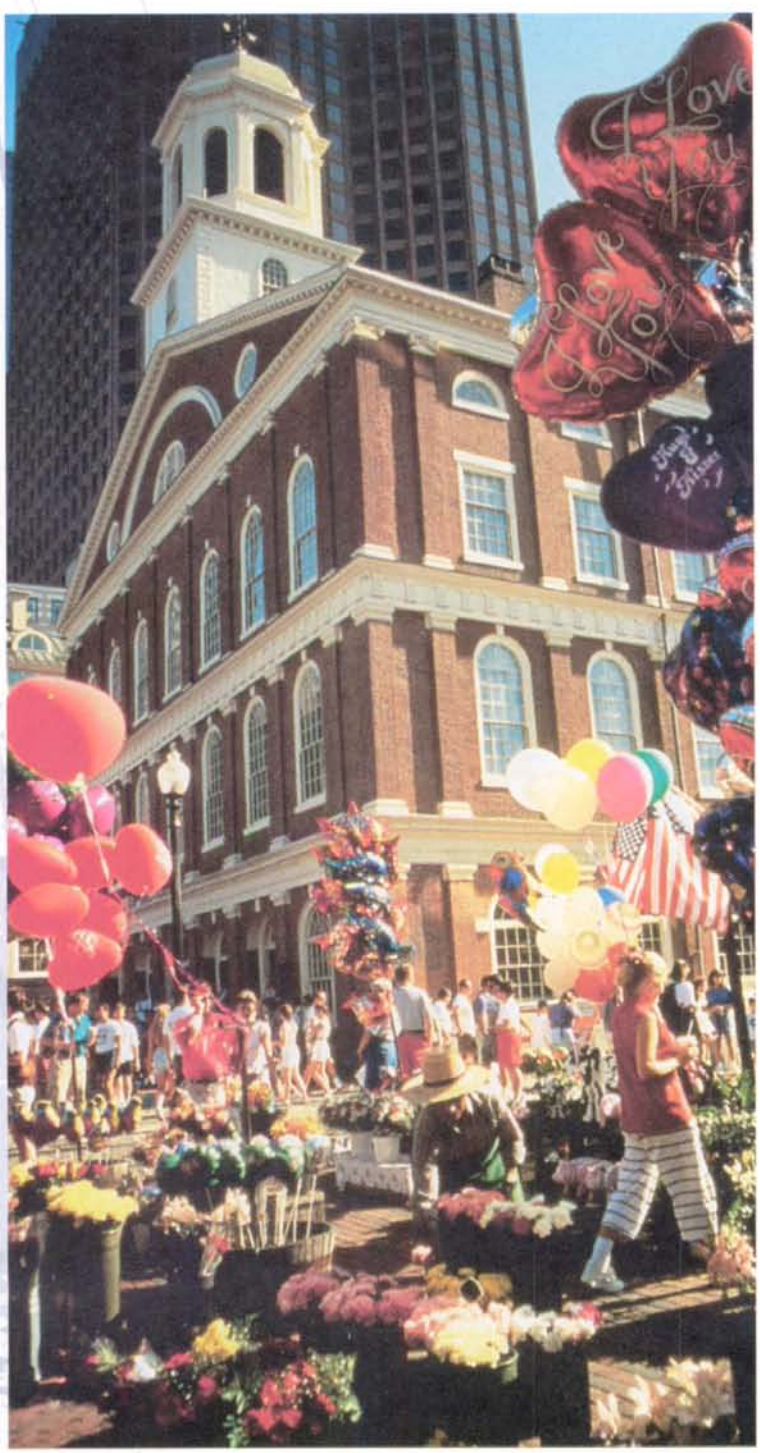
COUNCIL INTEREST DISCUSSION SESSIONS

11 Professional Section Councils have elected to conduct a Discussion Session focusing on a topic of interest to the members of the various councils. Check your Council home page for more information on its session **www.diabetes.org**.

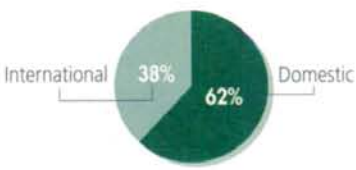
WHY SHOULD YOU ATTEND?

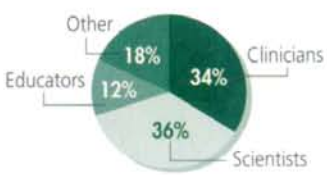
- Multiple educational sessions focusing on the latest in clinical and basic research.
- Targeted workshops exploring critical issues led by experts in diabetes.
- A continuous learning environment featuring in-depth sessions and open forums.
- Network, interact, and exchange information with your colleagues from all over the world.

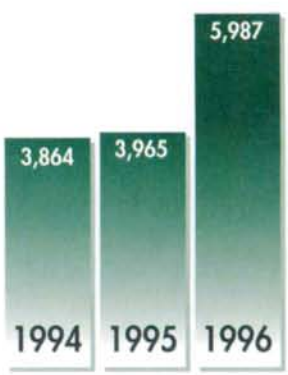
For more detailed program information visit the Association's website at: www.diabetes.org/am97



ATTENDANCE BREAKDOWN AND HISTORY







57th Scientific Sessions
Boston, Massachusetts
June 21-24, 1997

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Phone: (703) 549-1500 x2453
Fax: (703) 299-5513
E-mail: meetings@diabetes.org.

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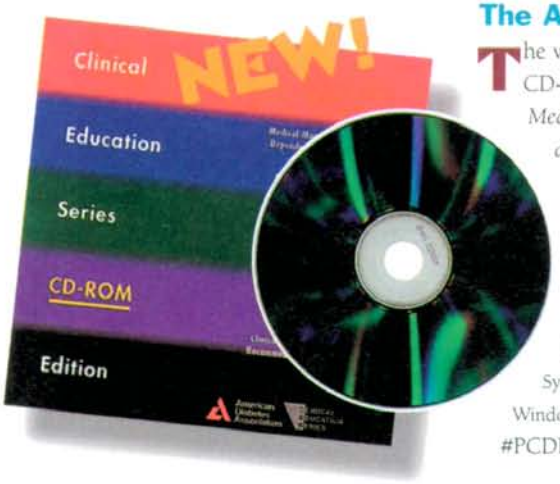
American Diabetes Association.

Clinical Education Series Goes Hi-Tech



The ADA Clinical Education Series on CD-ROM

The world's most comprehensive diabetes treatment information can be at your fingertips in seconds with CD-ROM technology! Presenting the first all-in-one database of diabetes treatment information. Includes: *Medical Management of Type I Diabetes; Medical Management of Type II Diabetes; Therapy for Diabetes Mellitus and Related Disorders, 2nd Ed.; Medical Management of Pregnancy Complicated by Diabetes, 2nd Ed.;* plus ADA's *Clinical Practice Recommendations 1995.*

All of these titles are on one compact disc, allowing for quick searches of key terms and phrases across all titles in the database. It also features a "hypertext link" giving you instantaneous browsing between text, references, and illustrations. Best of all, it's easy to install and use. You need no previous familiarity with CD-ROM technology. If you do have questions or need assistance, there's a toll-free line to technical experts who will be happy to help. Works in Windows or Macintosh environment.

System requirements: Macintosh - 68020 or greater processor, System 7.0 or greater, 2MB RAM (4MB recommended); Windows - 386 or 486 processor (486 recommended), Windows 3.1 or greater, 4MB RAM. 1995.

#PCDROM1 • ***Nonmember: $124.95; Member: $ 99.95***

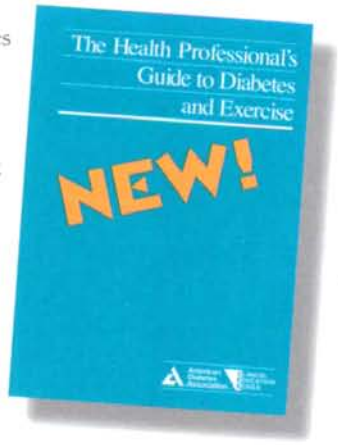
New Titles Give Health Pros Practical Treatment Advice

Intensive Diabetes Management

An all-inclusive "how to" manual on implementing tight diabetes control in your practice. Written by a team of experts with first-hand DCCT experience, this valuable guide provides you with the practical information needed to implement intensive management. Softcover; approximately 112 pages.

Contents: The Team Approach to Intensive Management • Education • Rationale for Intensification • Multiple-Component Insulin Regimens • Monitoring • Nutrition • Psychological Support and Behavioral Issues • Follow-Up and Preventive Care Guidelines • Alternative Insulin Delivery Systems • Complications and Adverse Effects • Resources

#PMIDM • Nonmember: $37.50; Member: $29.95



The Health Professional's Guide to Diabetes and Exercise

The first comprehensive guide to prescribing exercise as a therapy in managing diabetes. This valuable book examines the physiological effects of exercise and its metabolic benefits for patients with diabetes. And it covers dietary management and insulin adjustment, as well as behavioral and compliance issues as they relate to the exercise prescription.

The Handbook also delves into special situations such as prescribing exercise for patients with complications, pregnant patients, and older adults. An invaluable resource for anyone treating patients with diabetes! Softcover; approximately 350 pages.

Contents: Basic Considerations • The Treatment Plan • Exercise in Patients with Diabetic Complications • Special Patient Groups • Different Sports: Practical Advice and Experience

#PMHDE • Nonmember: $49.95; Member: $39.95

To order, call 1-800/ADA-ORDER or send in the coupon below:

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❑ NO. I'm not ordering right now, but please send me a free catalog.

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up to $30.00	add $3.00
$30.01–$50.00	add $4.00
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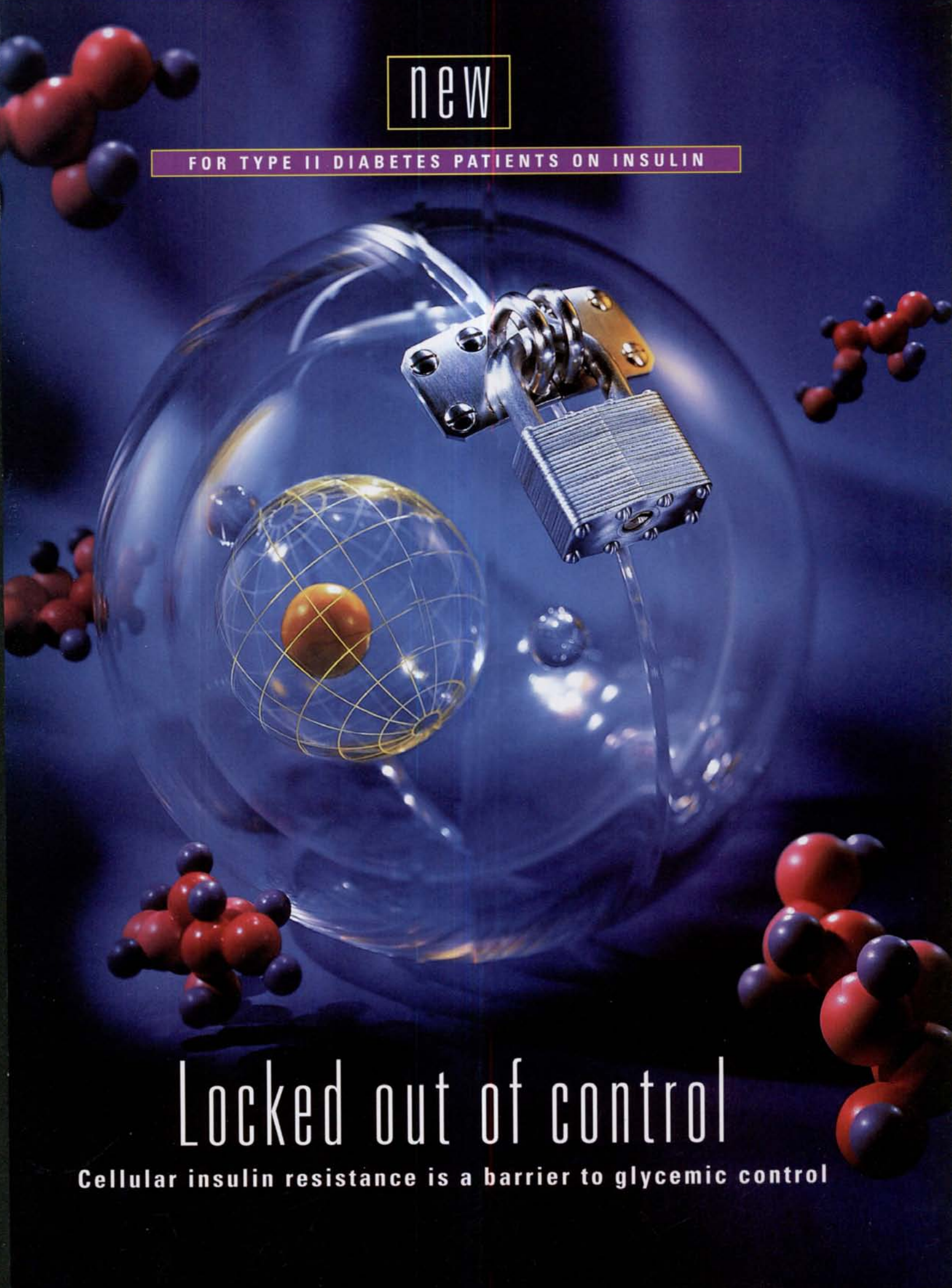
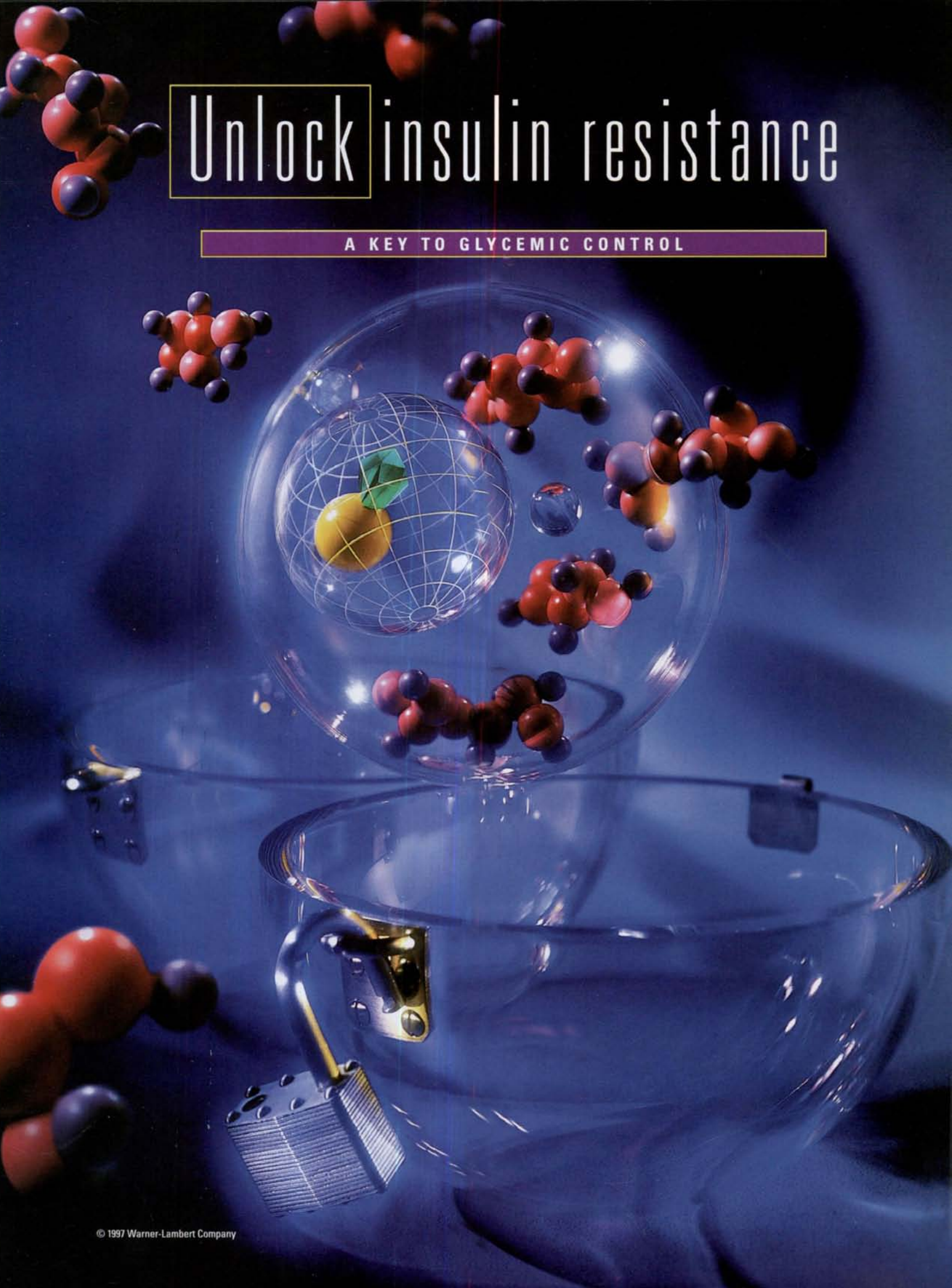
American Diabetes Association.


new
FOR TYPE II DIABETES PATIENTS ON INSULIN
Locked out of control
Cellular insulin resistance is a barrier to glycemic control



ONCE-DAILY

new REZULIN™

TROGLITAZONE

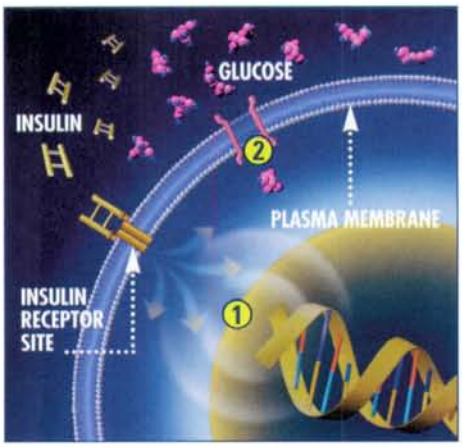
200, 400 MG TABLETS

The first agent that directly reduces insulin resistance through a unique nuclear mechanism

First in a new class—THIAZOLIDINEDIONES

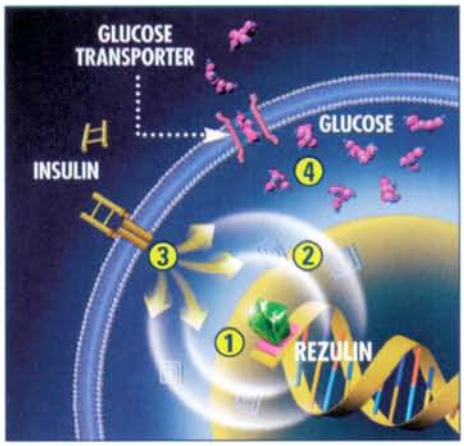
- Enhances insulin action in skeletal muscle, adipose tissue, and the liver
- It is not chemically or functionally related to the sulfonylureas, biguanides, or α-glucosidase inhibitors
- Indicated for use in insulin-treated Type II diabetes patients inadequately controlled (HbA_{1c} > 8.5%) with insulin despite over 30 units per day in multiple injections

Works at the cellular level to treat mechanisms of insulin resistance



Insulin resistance

1. In insulin resistance, postreceptor signaling is diminished.
2. Diminished signaling results in poor uptake, utilization, and storage of glucose.



The action of Rezulin

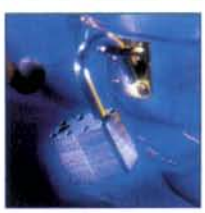
1. Rezulin binds to and activates a nuclear receptor (PPAR) that specifically regulates gene transcription.
2. As a result of this activation, specific proteins that play an important role in regulating carbohydrate and lipid metabolism are expressed.
3. Expression of these proteins improves insulin action in the cell, resulting in increased signaling.
4. It also results in the transport of more glucose into the cell for utilization and storage.

Rezulin should not be used in Type I diabetes or for the treatment of diabetic ketoacidosis.
Management of Type II diabetes should also include diet control, weight loss, and exercise.
Prior to initiation of Rezulin therapy, correctable causes of poor glycemic control should be sought and treated.

FOR TYPE II DIABETES PATIENTS ON INSULIN

new REZULIN™

Unlocks insulin resistance



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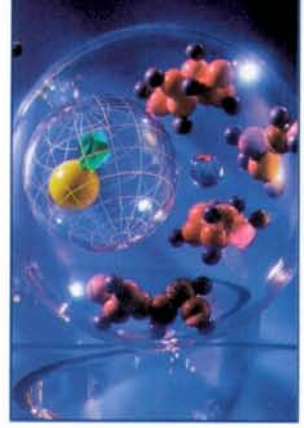
new

ONCE-DAILY

REZULIN™

TROGLITAZONE

200, 400 MG TABLETS



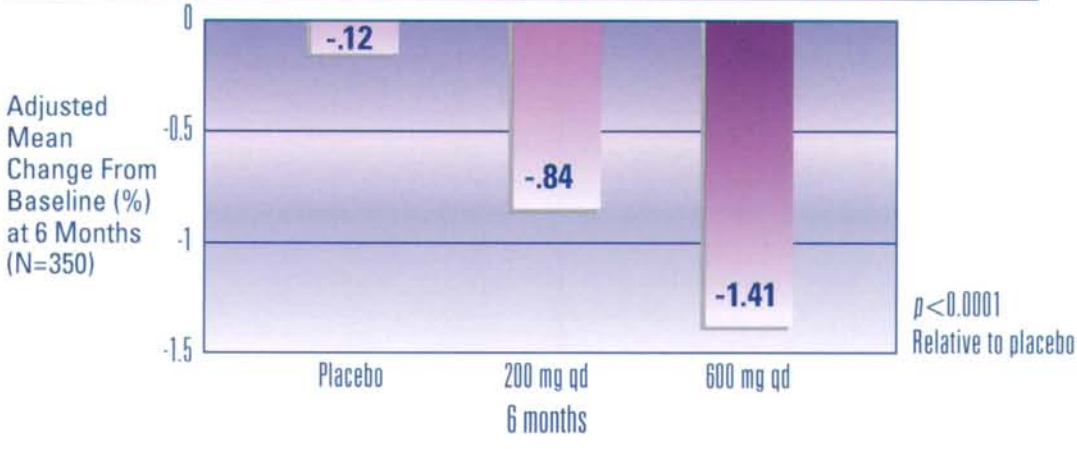
A KEY TO CONTROL

Consistent improvement in glycemic control

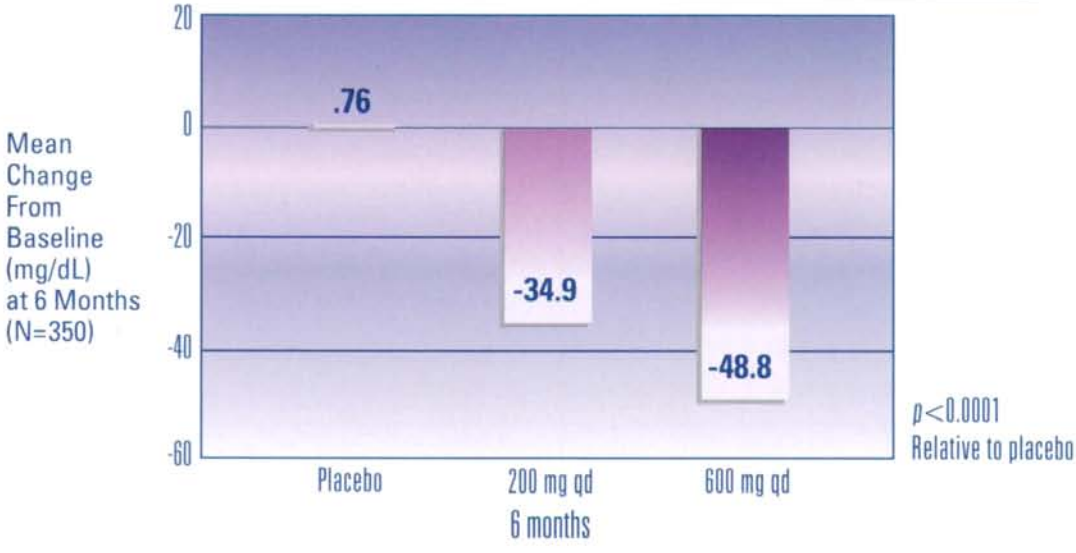
STUDY POPULATION

- Insulin-requiring, Type II diabetes patients with mean insulin dose of 73 units/day (range = 27 to 143), FSG of 216 mg/dL, and HbA_{1c} of 9.42 (range = 7.04 to 12.48)

SIGNIFICANT REDUCTIONS IN GLYCOSYLATED HEMOGLOBIN (HbA_{1c})



SIGNIFICANT REDUCTIONS IN FASTING SERUM GLUCOSE (FSG)



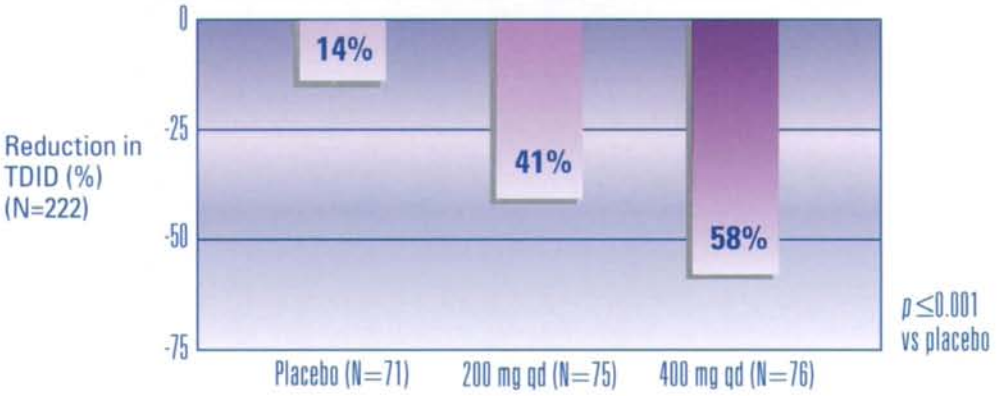
- Reductions in FSG were observed within the first 2 to 4 weeks of treatment with Rezulin

Reduces insulin dose, maintains or improves glycemic control

STUDY POPULATION

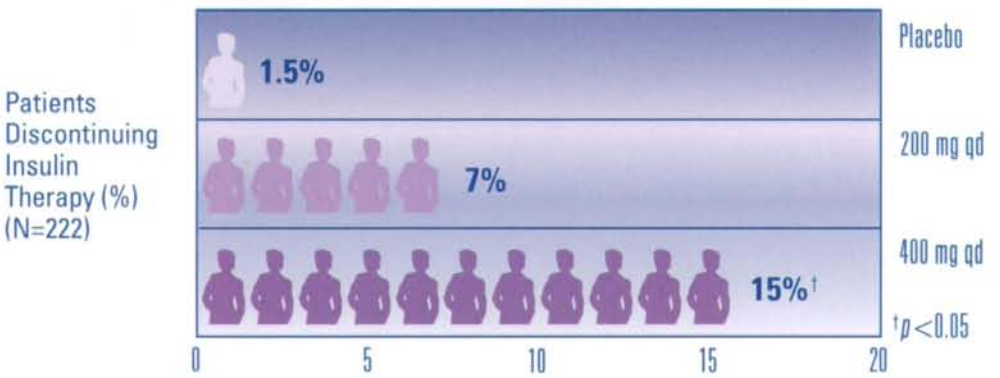
- Insulin-requiring, Type II diabetes patients with mean insulin dose of 72 units/day (range = 27 to 145), FSG of 225 mg/dL, and HbA_{1c} of 9.2 (range = 6.5 to 13.9)

REDUCTION IN TOTAL DAILY INSULIN DOSE (TDID) AT 6 MONTHS



- These reductions in TDID were achieved while maintaining or improving glycemic control*

PATIENTS DISCONTINUING INSULIN THERAPY (%) AT 6 MONTHS



- 41% of patients in the 400-mg group decreased their insulin injection frequency on average from 3 to 1 injections per day; 19% of placebo-treated patients decreased their injection frequency on average from 3 to 2 injections per day

The clinical effects of Rezulin occur independent of weight loss

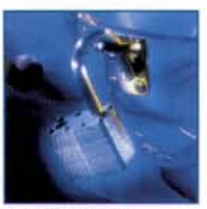
Management of Type II diabetes should also include diet control, weight loss, and exercise.

*Goals for glycemic control should be achieved prior to insulin reduction or discontinuation.

FOR TYPE II DIABETES PATIENTS ON INSULIN

new REZULIN™

Unlocks insulin resistance



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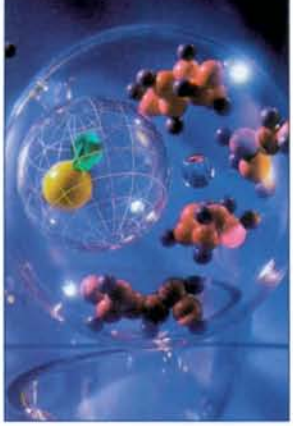
ONCE-DAILY

REZULIN™

TROGLITAZONE

200, 400 MG TABLETS



A KEY TO CONTROL

Side effects comparable to placebo

Excellent safety and tolerability profile established in controlled clinical trials

Comparable adverse events ≥5% reported for Rezulin- or placebo-treated patients

	PERCENTAGE OF PATIENTS	
	Placebo (N = 492)	Rezulin (N = 1450)
Infection	22	18
Headache	11	11
Pain	14	10
Accidental Injury	6	8
Asthenia	5	6
Dizziness	5	6
Back Pain	4	6
Nausea	4	6
Rhinitis	7	5
Diarrhea	6	5
Urinary Tract Infection	6	5
Peripheral Edema	5	5
Pharyngitis	4	5

Hypoglycemia has not been observed during the administration of Rezulin as monotherapy

- Patients receiving Rezulin in combination with insulin may be at risk for hypoglycemia and a reduction in the dose of insulin may be necessary

Drug Interactions

- Cholestyramine reduces the absorption of troglitazone by approximately 70%; thus, coadministration of cholestyramine and Rezulin is not recommended
- Rezulin decreases plasma concentrations of terfenadine and its active metabolite by 50% to 70% and may reduce the effectiveness of terfenadine
- Administration of Rezulin with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%. These changes could result in loss of contraception

Once-daily dosing may enhance compliance

Usual dose: 400 mg once daily with any meal

QD DOSAGE AND TITRATION GUIDELINES

Take With a Meal

Initial Dose

200 mg

Usual Dose

400 mg

- For patients not responding adequately, Rezulin dose should be increased at 2 to 4 weeks to 400 mg once daily. Maximum dose is 600 mg qd. See Dosage and Administration in Brief Summary of Prescribing Information
- The current insulin dose should be continued upon initiation of Rezulin therapy. It is recommended that the insulin dose be decreased by 10% to 25% when fasting plasma glucose levels decrease to less than 120 mg/dL in patients receiving concomitant insulin and Rezulin. Further adjustments should be individualized based on individual glucose-lowering response

Well tolerated in many different types of patients

- No differences in effectiveness and safety were observed between patients 65 and over and younger patients*
- No dose adjustments in patients with renal dysfunction
- There are no known interactions between Rezulin and laboratory tests
- Rezulin should be used with caution in patients with hepatic dysfunction

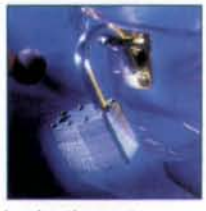
In premenopausal anovulatory patients with insulin resistance, Rezulin treatment may result in resumption of ovulation. **These patients may be at risk for pregnancy.**

Rezulin has not been tested in patients with New York Heart Association (NYHA) Class III and IV cardiac status; therefore, caution is advised in administering Rezulin to these patients.

*Safety and effectiveness in pediatric patients have not been established.

FOR TYPE II DIABETES PATIENTS ON INSULIN

new REZULIN™



Unlocks insulin resistance

Please see Brief Summary of Prescribing Information on last page of this advertisement.

ONCE-DAILY

new REZULIN™

TROGLITAZONE

200, 400 MG TABLETS

UNLOCKS INSULIN RESISTANCE

BRIEF SUMMARY

Consult Package Insert for full Prescribing Information.

INDICATIONS AND USAGE

Rezulin is indicated for use in patients with type II diabetes currently on insulin therapy whose hyperglycemia is inadequately controlled (HbA_{1C} >8.5%) despite insulin therapy of over 30 units per day given as multiple injections.

Management of type II diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient. This is important not only in the primary treatment of type II diabetes, but in maintaining the efficacy of drug therapy. Prior to initiation of Rezulin therapy, secondary causes of poor glycemic control, eg, infection or poor injection technique, should be investigated and treated.

CONTRAINDICATIONS

Rezulin is contraindicated in patients with known hypersensitivity or allergy to Rezulin or any of its components.

PRECAUTIONS

General

Because of its mechanism of action, Rezulin is active only in the presence of insulin. Therefore, Rezulin should not be used in type I diabetes or for the treatment of diabetic keto-acidosis.

Hepatic: During all clinical studies in North America (N=2510 patients), a total of 20 Rezulin-treated patients were withdrawn from treatment because of liver function test abnormalities. Two of the 20 patients developed reversible jaundice. Both had liver biopsies which were consistent with an idiosyncratic drug reaction (see ADVERSE REACTIONS, Laboratory Abnormalities).

Hypoglycemia: Patients receiving Rezulin in combination with insulin may be at risk for hypoglycemia and a reduction in the dose of insulin may be necessary. Hypoglycemia has not been observed during the administration of Rezulin as monotherapy and would not be expected based on the mechanism of action.

Ovulation: In premenopausal anovulatory patients with insulin resistance, Rezulin treatment may result in resumption of ovulation. **These patients may be at risk for pregnancy.**

Hematologic: Across all clinical studies, hemoglobin declined by 3 to 4% in troglitazone-treated patients compared with 1 to 2% in those treated with placebo. White blood cell counts also declined slightly in troglitazone-treated patients compared to those treated with placebo. These changes occurred within the first four to eight weeks of therapy. Levels stabilized and remained unchanged for up to two years of continuing therapy.

These changes may be due to the dilutional effects of increased plasma volume and have not been associated with any significant hematologic clinical effects (See ADVERSE REACTIONS, Laboratory Abnormalities).

Information for Patients

Rezulin should be taken with meals. If the dose is missed at the usual meal, it may be taken at the next meal. If the dose is missed on one day, the dose should not be doubled the following day.

It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. During periods of stress such as fever, trauma, infection, or surgery, insulin requirements may change and patients should seek the advice of their physician.

When using combination therapy with insulin, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Drug Interactions

Cholestyramine: Concomitant administration of cholestyramine with Rezulin reduces the absorption of troglitazone by approximately 70%; thus, coadministration of cholestyramine and Rezulin is not recommended.

Acetaminophen: Coadministration of acetaminophen and Rezulin does not alter the pharmacokinetics of either drug.

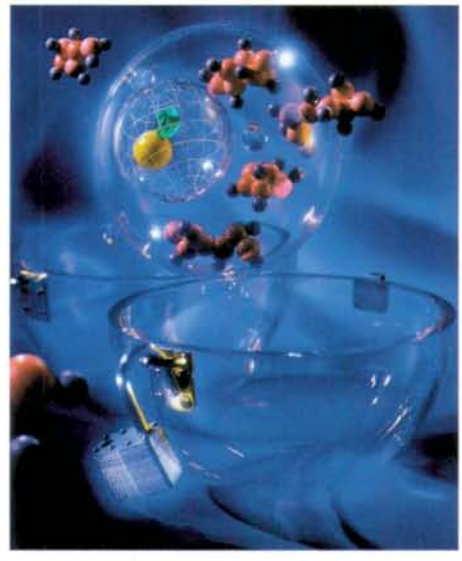
Warfarin: Rezulin has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Sulfonylureas: Coadministration of Rezulin with glyburide does not appear to alter troglitazone or glyburide pharmacokinetics, but may further decrease fasting plasma glucose. There are insufficient data on the use of Rezulin with sulfonylureas to establish the efficacy of this combination.

Metformin: No information is available on the use of Rezulin with metformin.

Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in Rezulin-treated patients with type II diabetes mellitus.

Terfenadine: Coadministration of Rezulin with terfenadine decreases plasma concentrations of terfenadine and its active metabolite by 50 to 70% and may reduce the effectiveness of terfenadine.



Oral Contraceptives: Administration of Rezulin with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%. These changes could result in loss of contraception. The above interactions with terfenadine and oral contraceptives suggest that troglitazone may induce drug metabolism by CYP3A4. These findings should be considered when prescribing other CYP3A4 substrates such as cyclosporine, tacrolimus and some HMG-CoA reductase inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Troglitazone was administered daily for 104 weeks to male rats at 100, 400, or 800 mg/kg and to female rats at 25, 50, or 200 mg/kg. Maximum plasma troglitazone AUC values based on parent compound represent exposures 12- and 47-fold higher for male and female rats, respectively, than human exposure of 400 mg daily. Troglitazone was not carcinogenic in male rats at any dose tested. In female rats, there was a statistically significant increase in sarcomatous tumors at the high dose (47-fold greater than estimated human exposure of parent compound). However, these findings are of unknown clinical relevance as this dose was associated with excessive mortality and is considered to have surpassed the maximum tolerated dose. No tumors of any type were increased in rats at 25 and 50 mg/kg at exposures of 5- to 14-fold higher than in humans based on AUC of parent compound. In a 104-week study in mice given 50, 400, or 800 mg/kg, incidence of hemangiosarcoma was increased in females at 400 mg/kg and in both sexes at 800 mg/kg; incidence of hepatocellular carcinoma was increased in females at 800 mg/kg. The lowest dose with increased tumor incidence (400 mg/kg) was associated with AUC values of parent compound that were at least 16-fold higher than the human exposure. No tumors of any type were increased in mice at 50 mg/kg at exposures 2- to 4-fold higher than in humans based on AUC of parent compound.

Troglitazone was neither mutagenic in bacteria nor clastogenic in bone marrow of mice. Equivocal increases in chromosome aberrations were observed in an *in vitro* Chinese hamster lung cell assay. In mouse lymphoma cell gene mutations assays, results were equivocal when conducted with a microtiter technique and negative with an agar plate technique. A liver unscheduled DNA synthesis assay in rats was negative.

No adverse effects on fertility or reproduction were observed in male or female rats given 40, 200, or 1000 mg/kg daily prior to and throughout mating and gestation. AUC at these doses was estimated to be 2- to 8-fold higher than the human exposure.

Pregnancy

Pregnancy Category B. Troglitazone was not teratogenic in rats given up to 2000 mg/kg or rabbits given up to 1000 mg/kg during organogenesis. Compared to human exposure of 400 mg daily, estimated exposures based on AUC at these doses were up to 8-fold higher in rats and up to 6-fold higher in rabbits. Body weights of fetuses and offspring of rats given 2000 mg/kg during gestation were decreased. Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats given 40, 200, or 1000 mg/kg during late gestation and lactation periods; no effects were observed in offspring of rats given 10 or 20 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Rezulin should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers

It is not known whether troglitazone is secreted in human milk. Troglitazone is secreted in the milk of lactating rats. Because many drugs are excreted in human milk, Rezulin should not be administered to a breast-feeding woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Twenty-two percent of patients in clinical trials of Rezulin were 65 and over. No differences in effectiveness and safety were observed between these patients and younger patients.

Use in Patients With Heart Failure

Heart enlargement without microscopic changes has been observed in rodents at exposures exceeding 14 times the AUC of the 400 mg human dose. Serial echocardiographic evaluations in monkeys treated chronically at maximum achievable exposures (3-5 times the human exposure at the 400 mg dose) did not reveal changes in heart size or function. In a 2-year echocardiographic clinical study using 600 to 800 mg/day of Rezulin in patients with type II diabetes, no increase in left ventricular mass or decrease in cardiac output was observed. The methodology employed was able to detect a change of about 10% or more in left ventricular mass.

In animal studies, troglitazone treatment was associated with increases of 6% to 15% in plasma volume. In a study of 24 normal volunteers, an increase in plasma volume of 6% to 8% compared to placebo was observed following 6 weeks of troglitazone treatment.

No increased incidence of adverse events potentially related to volume expansion (eg, congestive heart failure) have been observed during controlled clinical trials. However, patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during clinical trials. Therefore, caution is advised during the administration of Rezulin to patients with NYHA Class III or IV cardiac status.

ADVERSE REACTIONS

In general, Rezulin is well-tolerated. Two patients in the clinical studies developed reversible jaundice with findings on liver biopsy consistent with idiosyncratic drug reaction (See PRECAUTIONS, General).

The overall incidence and types of adverse reactions reported in placebo-controlled clinical trials for Rezulin-treated patients and placebo-treated patients are shown in Table 1. In patients treated with Rezulin in glyburide-controlled studies (N=550) or uncontrolled studies (N=510), the safety profile of Rezulin appeared similar to that displayed in Table 1. The incidence of withdrawals during clinical trials was similar for patients treated with placebo or Rezulin (4%).

TABLE 1. North American Placebo-Controlled Clinical Studies: Adverse Events Reported at a Frequency ≥ 5% of Rezulin-Treated Patients (% of Patients)

	Placebo N = 492	Rezulin N = 1450
Infection	22	18
Headache	11	11
Pain	14	10
Accidental Injury	6	8
Asthenia	5	6
Dizziness	5	6
Back Pain	4	6
Nausea	4	6
Rhinitis	7	5
Diarrhea	6	5
Urinary Tract Infection	6	5
Peripheral Edema	5	5
Pharyngitis	4	5

Types of adverse events seen when Rezulin was used concomitantly with insulin (N=543) were similar to those during Rezulin monotherapy (N=1731), although hypoglycemia occurred on insulin combination therapy (see PRECAUTIONS).

Laboratory Abnormalities

Hematologic: Small decreases in hemoglobin, hematocrit, and neutrophil counts (within the normal range) were more common in Rezulin-treated than placebo-treated patients and may be related to increased plasma volume observed with Rezulin treatment. Hemoglobin decreases to below the normal range occurred in 5% of Rezulin-treated and 4% of placebo-treated patients.

Lipids: Small changes in serum lipids have been observed (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects in package insert for full prescribing information).

Serum Transaminase Levels: During controlled clinical trials, 2.2% of Rezulin-treated patients had reversible elevations in AST or ALT greater than 3 times the upper limit of normal, compared with 0.6% of patients receiving placebo. Hyperbilirubinemia (>1.25 upper limit of normal) was found in 0.7% of Rezulin-treated patients compared with 1.7% of patients receiving placebo. In the population of patients treated with Rezulin, mean and median values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline, while values for LDH were increased slightly (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

The current insulin dose should be continued upon initiation of Rezulin therapy. Rezulin therapy should be initiated at 200 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of Rezulin should be increased after approximately 2 to 4 weeks. The usual dose of Rezulin is 400 mg once daily. The maximum recommended daily dose is 600 mg. It is recommended that the insulin dose be decreased by 10% to 25% when fasting plasma glucose concentrations decrease to less than 120 mg/dL in patients receiving concomitant insulin and Rezulin. Further adjustments should be individualized based on glucose-lowering response. Rezulin should be taken with a meal.

Patients With Renal Insufficiency

Dose adjustment in patients with renal insufficiency is not required (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism in package insert for full prescribing information).

Patients With Hepatic Impairment

Rezulin should be used with caution in patients with hepatic disease (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism in package insert for full prescribing information).

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Agenda:

Scope of the Problem
Maureen I. Harris, Ph.D., MPH;
Susceptibility of Complications: Ethnic and Racial Variations
Lewis H. Kuller, MD, DrPH
Prevention of Complications in the Management of IDDM: Blood Glucose Control
Robert A. Rizza, MD
Diagnosis and Management of Diabetic Dyslipidemia
Frederick L. Dunn, MD
Nephropathy in NIDDM
Michael W. Steffes, MD, Ph.D.
Diagnosis and Classification of Neuropathy
Eva L. Feldman, MD, Ph.D.
Treatment of Neuropathy
Douglas A. Greene, MD
Agenda Strategies to Prevent Lower Extremity Amputations
Lee J. Sanders, DPM
Treatment of Coronary Artery Disease
Richard W. Nesto, MD
The Role of Primary Care Physicians in the Detection of Retinopathy
Frederick L. Ferris III, MD
Future Therapies in Diabetes Care
Jay S. Skyler, MD

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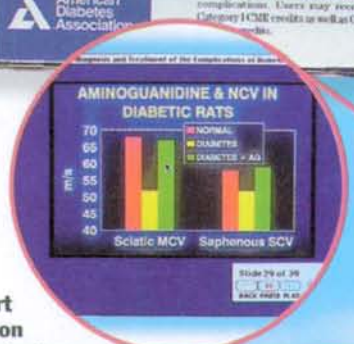

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ArtAssist® Case Report

Diabetic limb salvage using the Arterial Assist Device. . . ArtAssist*

Paul S. van Bemmelen, MD, PhD, Port Jefferson, NY and
Gerald J. Furst, DPM, Port Jefferson, NY

Patient

- 66 Year Old Male
- 35 Year Hx of Diabetes
- Renal Failure
- Contralateral Tibial Bypass
- Poor Ambulation
- Small Vessel Disease

Past Therapies

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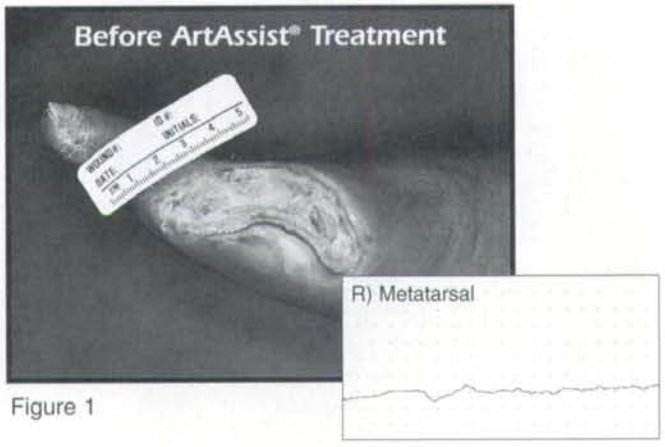

Figure 1

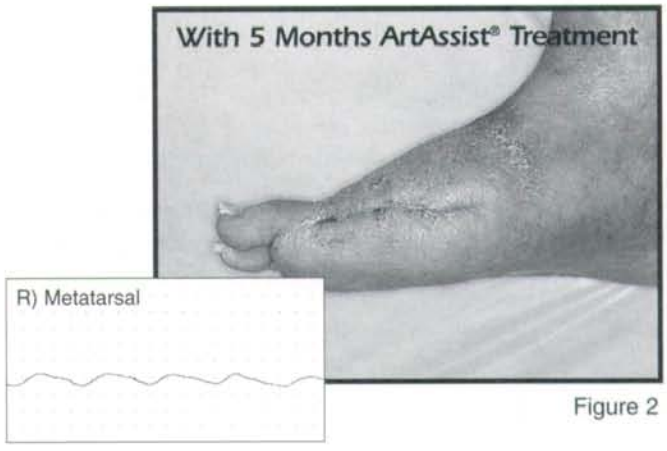

Figure 2

Pulse Volume Recordings

A 66 year old man with a 35 year history of diabetes (NIDDM) and chronic renal failure (peritoneal dialysis) presented with dry necrosis of his right great toe. He ambulated very little outside of his home and he had previously undergone a tibial bypass of the opposite leg. He was being treated with platelet released growth factors for poor healing of his left distal ankle incision. Ankle blood pressure was not obtainable due to non-compressibility, but wave forms were consistent with disease of the small vessels distal to the knee. The metatarsal pulse volume recording[1] is shown (Fig. 1) and is essentially flat. Toe-pressure was in the ischemic range.

The patient underwent repeated selective digital intra-arterial angiography, which demonstrated patent arteries to the level of the ankle only, without named run-off vessels in the foot. After explaining the poor chances of healing of a toe amputation to the patient, he underwent amputation of the right great toe and metatarsal head. Treatment with the ArtAssist device was not available at that time. The toe amputation failed and complete dehiscence, with exposed metatarsal bone was apparent in (Fig.1). Debridements and immediate treatment with growth factors were instituted. Further deterioration occurred slowly. Further revision foot amputation was not considered to be a worthwhile option and below-knee amputation would be the next surgical step.

Intermittent compression with the ArtAssist device was started two months after the toe amputation for at least 30 minutes, QID. Compression was well tolerated and after one week of home treatment, the patient noticed blood on his dressings. Slowly some granulation tissue appeared and the wound edges bled well with minor debridements. Improvement of the metatarsal pulse volume recording was noted. In view of the exposed metatarsal bone, with retracted skin edges, a further resection of Metatarsal I and the adjacent second toe was performed after two months of compression therapy. Oral antibiotics were given based on culture results. The growth factor treatment was stopped. The resulting wound is now healed by secondary intention (Fig.2). Further improvements occurred of the pulse volume recording at the metatarsal level, to the same amplitude as the bypassed side.

[1] Parks Flow-Lab

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Saturday

8:00am-10:00am

☐ADA96-100 **Symposium:** Pathophysiology & Risk Factors in Diabetic Foot Disease *2 tapes*

☐ADA96-101 **Oral Abstracts:** Abstracts 1-8 Complications, Nephropathy *2 tapes*

☐ADA96-102 **Symposium:** Immunobiology of Islet Transplantation *2 tapes*

☐ADA96-103 **Symposium:** Exercise and the Insulin Resistance Syndrome *2 tapes*

10:15am-11:30am

☐ADA96-104 **Discussion Session:** Council on Foot Care: Current Issues in Diabetic Foot Care

10:15am-12:15pm

☐ADA96-105 **Symposium:** Research on Education in Diabetes: Outcomes and Environment *2 tapes*

☐ADA96-106 **Symposium:** Impaired Glucose Tolerance: A Target for Intervention *2 tapes*

☐ADA96-107 **Symposium:** Regulated Vesticular Trafficking *2 tapes*

☐ADA96-108 **Symposium:** New Insights: Implications for NIDDM *2 tapes*

1:15pm-2:30pm

☐ADA96-109 **Discussion Session:** Council on Exercise: Exercise Therapy: Who are the Providers, What are the Costs, Who Pays?

☐ADA96-110 **Discussion Session:** Council on Education: Technology in Diabetes Education & Management: Help or Hindrance?

☐ADA96-111 **Discussion Session:** Provisional Council on Immunology, Immunogenetics, and Transplantation: Normalization of Assays for T & B Cell Autoantigens in IDDM

☐ADA96-112 **Discussion Session:** Council on Epidemiology & Statistics: Current Issues in Diabetes and Epidemiology *2 tapes*

2:45pm-4:45pm

☐ADA96-113 **Oral Abstracts:** Abstracts 37-44 Psychosocial/Behavioral *2 tapes*

☐ADA96-114 **Oral Abstracts:** Abstracts 9-16 Complications, Neuropathy *2 tapes*

☐ADA96-115 **State-of-the-Art Lecture:** Abstracts 25-30 Insulin Synthesis I *2 tapes*

☐ADA96-116 **Oral Abstracts:** Abstracts 17-24 Health Care Delivery *2 tapes*

☐ADA96-117 **State-of-the-Art Lecture:** Abstracts 31-36 Metabolism I *2 tapes*

☐ADA96-118 **Current Controversy:** Molecular Mimicry

Sunday

8:00am-10:00am

☐ADA96-119 **Symposium:** Family Focus: Involving the Family in Diabetes Management *2 tapes*

☐ADA96-120 **Symposium:** Novel Signaling Pathways *2 tapes*

☐ADA96-121 **Symposium:** Diabetes and Heart Disease *2 tapes*

☐ADA96-122 **Symposium:** Immunology and Autoimmunity *2 tapes*

10:15am-12:15pm

☐ADA96-123 President's Address, Banting Lecture

12:30pm-1:45pm

☐ADA96-124 **Discussion Session:** Council on Molecular, Cellular, & Biochemical Aspects of Diabetes: Opportunities for Academic and Industrial Collaboration: Careers and Training for Industry

☐ADA96-125 **Discussion Session:** Council on Behavioral Medicine & Psychology: Managed Care Issues for Behavioral Medicine

☐ADA96-126 **Discussion Session:** Council on Nutritional Science & Metabolism: Nurtition Education Resources: What Works for You? Any Changes Needed?

2:00pm-4:00pm

☐ADA96-127 **Mini-Symposium:** Pharmacodynamics of Thiazolidinediones *2 tapes*

☐ADA96-128 **Oral Abstracts:** Abstracts 53-60 Clinical Diabetes *2 tapes*

☐ADA96-129 **Oral Abstracts:** Abstracts 45-52 Complication, Retinopathy *2 tapes*

☐ADA96-130 **Poster Discussion Session:** Immunology *2 tapes*

☐ADA96-131 **Oral Abstracts:** Abstracts 61-68 Metabolism II *2 tapes*

☐ADA96-132 **Oral Abstracts:** Abstracts 69-76 Gene Regulation *2 tapes*

☐ADA96-133 **Current Controversy:** Xenotransplantation: Current Controversies in Correct Approaches *2 tapes*

4:15pm-6:15pm

☐ADA96-134 **State-of-the-Art Lecture:** Abstracts 85-90 Foot Care

☐ADA96-135 **Mini-Symposium:** Regulation of Glucose Fluxes: What Did We Learn From Transgenic Models? *2 tapes*

☐ADA96-136 **Oral Abstracts:** Abstracts 77-84 Transplantation *2 tapes*

☐ADA96-137 **Meet-the-Professor:** Endocrinology Training Program Issues in the Managed Care Era

☐ADA96-138 **Current Controversy:** Who Killed the Beta Cell?

☐ADA96-139 **Poster Discussion Session:** Pregnancy

☐ADA96-140 **Oral Abstracts:** Abstracts 91-98 Forms of Therapy/New Technology *2 tapes*

☐ADA96-141 **Oral Abstracts:** Abstracts 99-106 Genetics *2 tapes*

☐ADA96-142 **Poster Discussion Session:** Psychosocial/Behavioral I

Monday

8:00am-10:00am

☐ADA96-143 **Oral Abstracts:** Abstracts 113-120 Metabolism III *2 tapes*

☐ADA96-144 **State-of-the-Art Lecture:** Abstracts 107-112 Signal Transduction I *2 tapes*

☐ADA96-145 **Mini-Symposium:** Non-Nutrient Regulation of Insulin Secretion *2 tapes*

☐ADA96-146 **Symposium:** Update on New Treatments for the Complications of Diabetes *2 tapes*

☐ADA96-147 **Symposium:** Health Care Before and After Diabetic Pregnancy *2 tapes*

10:15am-11:30am

☐ADA96-148 Scientific Achievement Awards Presentation, Lilly Lecture

11:45am-2:00pm

☐ADA96-149 **Luncheon:** Senior Vice President's Address, Outstanding Health Professional Educator in Diabetes Award

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12:30pm-1:45pm

☐ADA96-150 **Discussion Session:** Council on Complications: DCCT Follow-up Study and New Data

☐ADA96-151 **Discussion Session:** Council on Diabetes in Pregnancy: Controversies in the Management of Gestational Diabetes

☐ADA96-152 **Discussion Session:** Council on Diabetes in Youth: Approaches to the Initial Management of New-onset Diabetes in Children

2:15pm-4:15pm

☐ADA96-153 **State-of-the-Art Lecture:** Abstracts 127-132 Lipids *2 tapes*

☐ADA96-154 **State-of-the-Art Lecture:** Abstracts 121-126 Metabolism IV *2 tapes*

☐ADA96-155 **Meet-the-Professor:** Development of Critical Pathways in Diabetes Management *2 tapes*

☐ADA96-156 **Poster Discussion:** Epidemiology *2 tapes*

☐ADA96-157 **Oral Abstracts:** Abstracts 141-148 Nutrition/Obesity/Exercise *2 tapes*

☐ADA96-158 **Oral Abstracts:** Abstracts 133-140 Insulin Synthesis II *2 tapes*

☐ADA96-159 **Poster Discussion Session:** Hormones, Not Insulin

☐ADA96-160 **Current Controversy:** Phosphatidylinositol 3- Kinase in GLUT4 Translocation *2 tapes*

☐ADA96-161 **Current Controversy:** How Does the MHC Cause Autoimmunity? *2 tapes*

4:15pm-5:30pm

☐ADA96-162 **Discussion Session:** Council on Endocrinology, Health Care Delivery & Public Health: Proceeding with Diabetes as a Public Health Issue: An Interactive Discussion *2 tapes*

4:30pm-6:30pm

☐ADA96-163 **Oral abstracts:** Abstracts 149-156 Diabetes Education *2 tapes*

☐ADA96-164 **Oral Abstracts:** Abstracts 157-164 Signal Transduction II *2 tapes*

☐ADA96-165 **Meet-the-Professor:** Global Perspectives in Diabetes Care

☐ADA96-166 **Oral Abstracts:** Abstracts 165-172 Complications, Macrovascular *2 tapes*

☐ADA96-167 **Oral Abstracts:** Abstracts 173-180 Insulin Action *2 tapes*

☐ADA96-168 **Meet-the-Professor:** African American Women with NIDDM

☐ADA96-169 **Mini-Symposium:** Type 1 Nutrition Practice Guidelines

Tuesday

8:00am-10:00am

☐ADA96-170 **Oral Abstracts:** Abstracts 181-188 Epidemiology *2 tapes*

☐ADA96-171 **Symposium:** Diabetes in a Managed Care Environment *2 tapes*

☐ADA96-172 **Symposium:** Issues in Intensive Therapy in Children and Adolescents *2 tapes*

☐ADA96-173 **Symposium:** Gene Therapy for Treatment of Disease *2 tapes*

☐ADA96-174 **Symposium:** Insulin Signaling to Glucose: An Update on Signal Transduction Pathways

10:15am-11:15am

☐ADA96-175 Kelly West Lecture

10:15am-12:15pm

☐ADA96-176 **Mini-Symposium:** Inhibitors of Insulin Action *2 tapes*

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☐ADA96-178 **Meet-the-Professor:** Update on Classification and Disgnosis of Diabetes Mellitus: Report from the Workgroup

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☐ADA96-180 **Oral Abstracts:** Abstracts 203-210 Pregnancy *2 tapes*

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TENURE-TRACK CLINICAL INVESTIGATORS

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The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is searching for two Clinical Investigators in the areas of Diabetology and Thyroidology (as specified below). Applicants should be licensed to practice medicine in the United States, and must be eligible for credentials to practice medicine at the National Institutes of Health. Furthermore, the ideal candidate would be Board Certified in both the specialty of Internal Medicine and the sub-specialty of Endocrinology and Metabolism. The extensive facilities of The Clinical Center will be available to carry out human studies. Candidates will be encouraged to collaborate with laboratory-based scientists at NIH. If appropriate, laboratory resources may also be made available to the successful candidates. However, the focus of these positions will be primarily to carry out patient-based research. In addition, the successful candidates will be expected to participate as faculty in the NIH Inter-Institute Training Program in Endocrinology and Metabolism. Applicants are invited to send a curriculum vitae, bibliography, brief description of future research plans (≤ 1000 words), and names and addresses of three references to: **DR. DEREK LE ROITH, CHAIRMAN, CLINICAL INVESTIGATOR SEARCH COMMITTEE, NATIONAL INSTITUTES OF HEALTH, BUILDING 10, ROOM 8S235A, 10 CENTER DRIVE, MSC 1770, BETHESDA, MD 20892-1770.**

Diabetes Mellitus and Obesity

The successful candidate will establish an independent program of patient-oriented research related to diabetes mellitus and/or obesity. This position will be located in the Diabetes Branch, NIDDK. Current areas of research within the Diabetes Branch focus upon the mechanisms of action of insulin and insulin-like growth factors, genetic factors predisposing to development of noninsulin-dependent diabetes mellitus, physiology of leptin, and obesity. However, the candidate will be free to pursue any area of research related to the areas of diabetes mellitus or obesity.

Thyroidology

The successful candidate will establish an independent program of patient-oriented research related to thyroid disease. This position will be located in the Molecular and Cellular Endocrinology Branch, NIDDK. Current areas of research within the Molecular and Cellular Endocrinology Branch include studies of the mechanisms of action of thyroid hormone, regulation of gene expression, thyroid hormone resistance, TSH-secreting pituitary tumors, and thyroid cancer. However, the candidate will be free to pursue any area of research related to the areas of thyroid disease.

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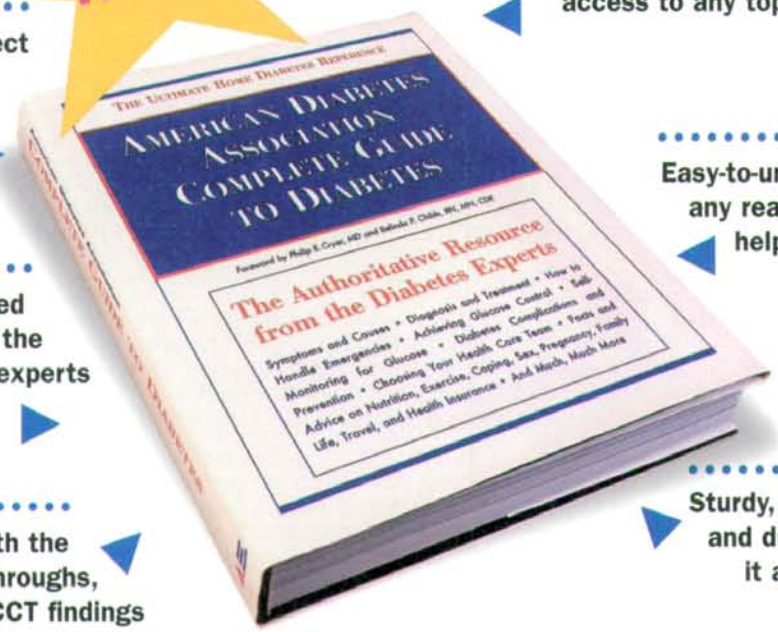

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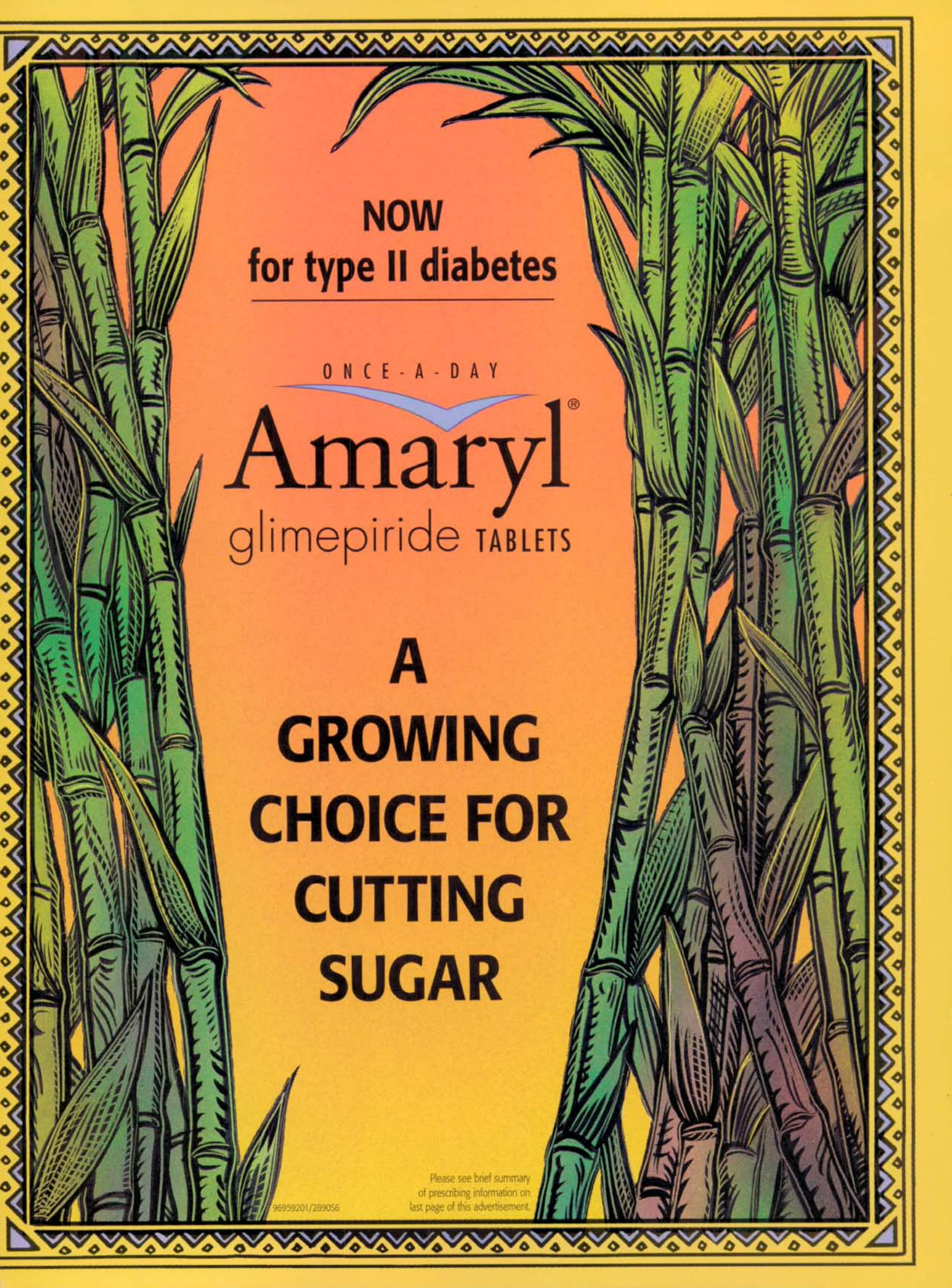
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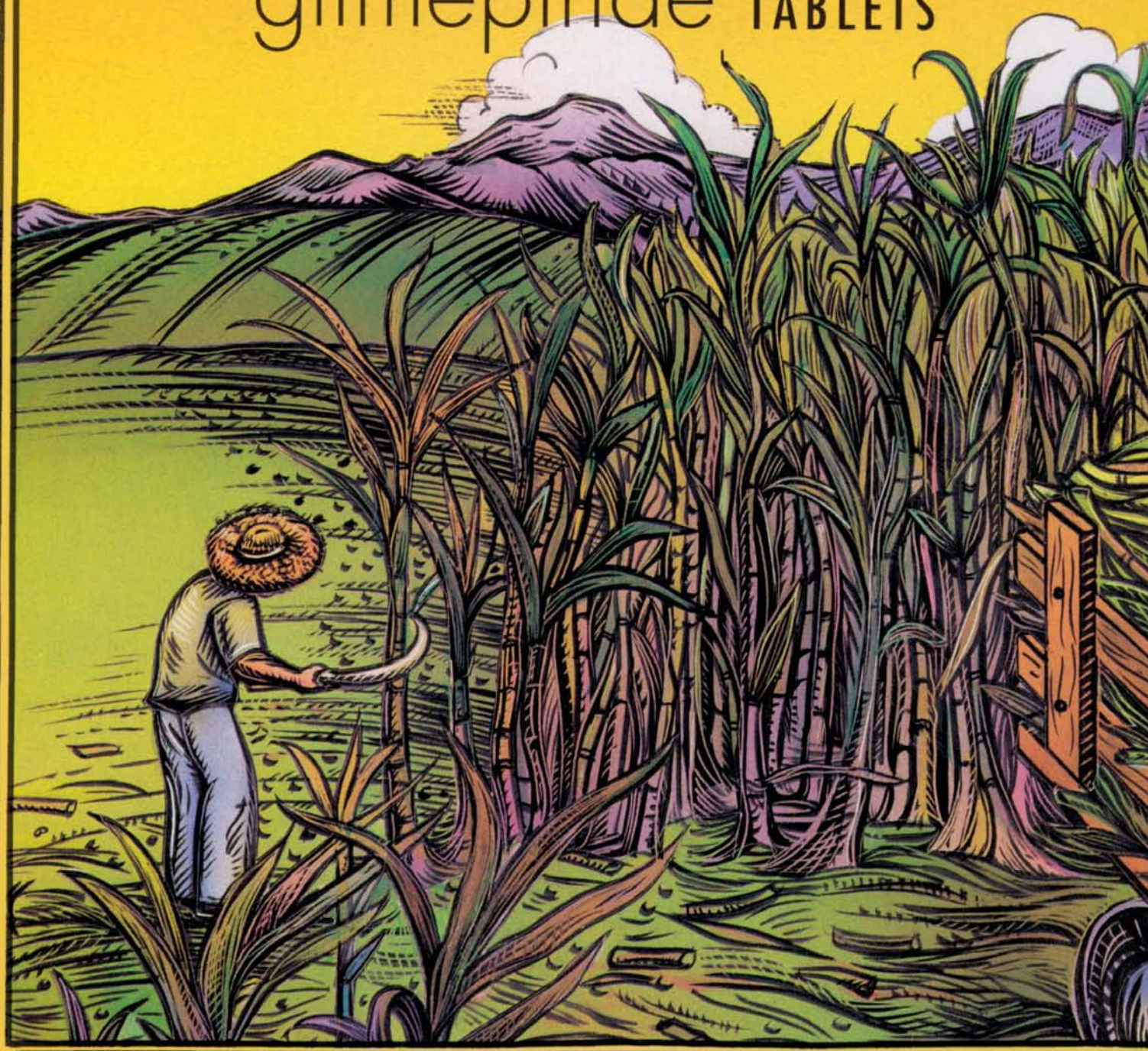

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†Combined use of Amaryl and insulin may increase the potential for hypoglycemia.

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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***).

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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, 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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