DIABETES CARE®

Instructions for Authors

CONTENT

Diabetes Care publishes original articles and reviews of human and clinical research intended to increase knowledge, stimulate research, and promote better management of people with diabetes mellitus. Emphasis is on human studies reporting on the pathophysiology and treatment of diabetes and its complications; genetics; epidemiology; psychosocial adaptation; education; and the development, validation, and application of accepted and new therapies. Topics covered are of interest to clinically oriented physicians, researchers, epidemiologists, psychologists, diabetes educators, and other professionals.

Original Articles report clinical investigation in areas relevant to diabetes. The following features are essential: hypothesis testing, suitable controls, appropriate statistical methods, clear reporting of results, and conclusions supported by the results. Papers will be judged on their uniqueness and importance.

Special Articles are scholarly discussions, perspectives, essays, opinions, hypotheses, and policy statements.

Technical Articles are descriptions and assessments of material and devices used for the care of patients with diabetes.

Short Reports are succinct case reports, observations relating to the practice of diabetology, and other brief communications.

Editorials consist of opinions of individuals or organizations on relevant topics by either the Editors or invited participants.

Letters & Comments include opinions on topics published in the journal or relating to diabetes in general.

REVIEW ISSUES

Of the 12 yearly issues of *Diabetes Care*, 4 are review issues. Articles in the review issues will have a common theme, each pertaining to a physiological or pathophysiological aspect of diabetes and related metabolic events. Future topics will be indicated on an Upcoming Review Issues page in the front of each review issue.

GENERAL GUIDELINES

Diabetes Care publishes only material that has not been printed previously or submitted elsewhere without appropriate annotation. In submitting an article, the author(s) must all sign a letter stating the following:

> We approve the submission of this paper to *Diabetes Care* for publication. We confirm that neither the manuscript submitted nor any part of it has been published or is being considered for publication elsewhere (abstracts excluded).
>
> In consideration of ADA reviewing my (our) submission, the undersigned author(s) transfers, assigns, or otherwise conveys all copyright ownership to ADA in the event the work is published.
>
> Signature of All Authors

Conflicts of interest or support of private interests must be clearly explained. All human investigation must be conducted according to the principles expressed in the Declaration of Helsinki.

 Manuscripts not conforming to these specifications will be returned to the author(s). The cover letter should also include the address and *telephone, telex,* and *telefax* numbers of the person responsible for negotiations concerning the manuscript. Authors are encouraged to suggest six possible reviewers for their manuscript.

All accepted manuscripts will be edited according to the *CBE Style Manual* (Council of Biology Editors, Inc., Bethesda, MD) and *The Chicago Manual of Style* (The University of Chicago Press, Chicago, IL) by ADA professional publications staff. The authors are responsible for all statements made in their articles or editorials, including any editing changes.

SPECIFICATIONS

Manuscripts. Five copies of the manuscript (original plus four photocopies of the entire manuscript including tables and figures) must

be submitted. If black-and-white graphs or charts are to be included, submit only one set of glossy prints; the remaining sets should be photocopies. If photographs are to be included, five sets must be submitted. Manuscripts must be typewritten (not photocopied), *double spaced (including references, legends, tables)* on one side of 8½ × 11-inch (21.6 × 27.9-cm) nonerasable white bond paper. Provide margins of at least 1 inch (2.5 cm) at top, bottom, and both sides of pages. Number pages consecutively in the upper right-hand corner. Arrange articles according to the following components.

Title page. Include title; short running title (~40 characters); first name, middle initial, and last name of each author, with highest academic degree; (in English); disclaimers (if any); name and address of author to whom affiliation correspondence and requests for reprints should be addressed; (acknowledgments of financial support and potential conflicts of interest); and 3–6 key words for indexing purposes (*diabetes* is not acceptable). (Acknowledge if paper was previously presented as an abstract.)

Abstract. An abstract of not more than 250 words should be included at the beginning of the article. It should be self-contained and understandable without reference to the text. The abstract should be submitted in a structured format and include the following 4 segments: *Objective*, purpose or hypothesis of study; *Research Design and Methods*, basic design, setting, number of participants and selection criteria, treatment or intervention, methods of assessment; *Results*, significant data found; *Conclusions*, validity and clinical applicability.

Terminology and style. The designations *insulin-dependent diabetes mellitus* (IDDM or type I) and *non-insulin-dependent diabetes mellitus* (NIDDM or type II) should be used when referring to the two major forms of diabetes mellitus. The term *diabetic* should not be used as a noun. The terms *men* and *women* are preferable to *males* and *females*.

Statistical methods should be identified. Acknowledgments of aid or criticism should be approved by the person whose help is being recognized.

Abbreviations. Use standard abbreviations and units recommended in the *CBE Style Manual*. Use of nonstandard abbreviations is discouraged, but if used, they should be defined the first time they appear in the text.

Units. Units should be in the Système International (SI) form (see table). Glycosylated hemoglobin should be expressed as percent of total as well as standard deviation from the mean of control levels.

Drug Names. Generic names should be used. Proprietary names may be given parenthetically with the first use of the generic name.

References. References should be cited consecutively. The reference list should be typed double spaced in the numerical order in which they are first cited in the text.

References should be cited according to the following examples. All authors should be cited, and inclusive page numbers should be provided. The journal titles should be abbreviated according to *Serial Sources for the BIOSIS (Biosciences Information Service) Data Base*.

Journal articles

Banting FG, Best C: The internal secretion of the pancreas. *J Lab Clin Med* 7:251–66, 1922

Books

Allen FM: *Studies Concerning Glycosuria and Diabetes*. Cambridge, MA, Harvard Univ. Press, 1913

Chapters in books

Stauffacher W, Renold AE: Pathophysiology of diabetes mellitus. In *Joslin's Diabetes Mellitus*. 11th ed. Marble A, White P, Bradley RF, Krall LP, Eds. Philadelphia, PA, Lea & Febiger, 1971, p. 35–98

Government publications

Fajan SS (Ed.): *Diabetes Mellitus*. Washington, DC, U.S. Govt. Printing Office, 1976 (DHEW publ. no. NIH 76-854).

References to articles that are "in press" must state the name of the journal. References to unpublished material, if essential, should be incorporated in the appropriate place in the text and not be included as part of the reference list. Written permission from authors of unpublished data should be obtained and submitted.

Authors are responsible for the accuracy of the references.

Illustrations. Figures should be professionally drawn and photographed. Materials (i.e., figures and tables) taken from other sources must be accompanied by written permission for reproduction obtained from the original publisher and author. They must be untrimmed, unmounted, unstapled, and no more than 12.7 × 7.3 cm (5 × 7"). Figures should include indication of error, e.g., SD or SE. Name(s) of author(s), figure number, and the top of the figure must be noted on the back of each illustration.

Tables. Tables should be typed double spaced on separate sheets, with number and title. Symbols for units should be confined to column headings. Abbreviations should be kept to a minimum and defined in the table legend. For footnotes, use the following symbols consecutively: *, †, ‡, §, ‖, ¶, **, ††, etc.

Short reports. Manuscripts submitted as Short Reports should not exceed 6 typewritten, double-spaced pages. Short Reports must include all parts as described under manuscript specifications.

Letters and comments. Letters and Comments should not exceed 3 typewritten, double-spaced pages.

Proceedings of symposia or meetings are published as supplements to *Diabetes Care*. Sponsoring groups are required to pay all costs. For more information, contact either the Editor or Beverly Brittan Cook, Director of Professional Publications, American Diabetes Association, National Center, 1660 Duke Street, Alexandria, VA 22314.

Review and action. All contributions, including solicited articles and symposia, are critically reviewed by the Editors and invited referees. Reviewers' comments are usually returned to authors. The decision of the Editors is final.

Editorial correspondence. All manuscripts and editorial correspondence should be addressed to David C. Robbins, MD, Editor, *Diabetes Care*, Medlantic Research Foundation, George Hyman Memorial Research Building, 108 Irving Street, NW, Washington, DC 20010.

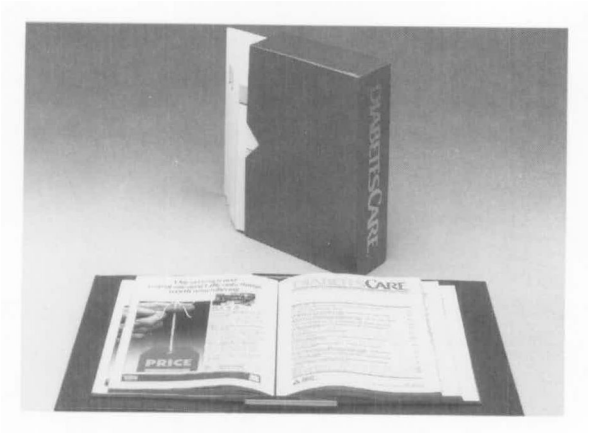
Articles for the review issues follow the same guidelines as for the regular issues, which are described herein. Although most articles for the review issues are invited by the editor, authors are welcome to submit manuscripts to Dr. Ralph A. DeFronzo, MD, Review Editor, *Diabetes Care*, Department of Medicine, Division of Diabetes, UTHSCSA, 7703 Floyd Curl Drive, San Antonio, TX 78284. Submitted manuscripts will be considered for relevant upcoming topics.

Correspondence concerning the copyediting and production of accepted manuscripts should be addressed to *Diabetes Care* Editorial Office, American Diabetes Association, National Center, 1660 Duke Street, Alexandria, VA 22314. Telephone: (703) 549-1500. FAX: (703) 683-2890.

TABLE 1
Système International (SI) units

Measurement	SI unit	Common unit	Conversion factors	
			Common → SI	SI → common
Acetone	μM	mg/dl	172	0.006
Aldosterone	pM	ng/dl	27.7	0.036
Amino acid fractionation				
Alanine	μM	mg/dl	112	0.009
α-Aminobutyric acid	μM	mg/dl	96.9	0.010
Arginine	μM	mg/dl	57.4	0.174
Asparagine	μM	mg/dl	75.7	0.132
Aspartic acid	μM	mg/dl	75.1	0.133
Citrulline	μM	mg/dl	57.1	0.018
Cystine	μM	mg/dl	41.6	0.024
Glutamic acid	μM	mg/dl	68.0	0.015
Glutamine	μM	mg/dl	68.4	0.015
Glycine	μM	mg/dl	133	0.008
Histidine	μM	mg/dl	64.5	0.016
Hydroxyproline	μM	mg/dl	76.3	0.013
Isoleucine	μM	mg/dl	76.2	0.013
Leucine	μM	mg/dl	76.2	0.013
Lysine	μM	mg/dl	68.4	0.015
Methionine	μM	mg/dl	67.0	0.015
Ornithine	μM	mg/dl	75.7	0.013
Phenylalanine	μM	mg/dl	60.5	0.017
Proline	μM	mg/dl	87.0	0.012
Serine	μM	mg/dl	95.2	0.011
Taurine	μM	mg/dl	79.9	0.013
Threonine	μM	mg/dl	84.0	0.012
Tryptophan	μM	mg/dl	49.0	0.020
Tyrosine	μM	mg/dl	55.2	0.018
Valine	μM	mg/dl	85.4	0.012
Amylase, enzymatic	U/L	U/L	1.00	1.00
Calcium	mM	mg/dl	0.250	4.00
Carbon dioxide content	mM	meq/L	1.00	1.00
Cholesterol	mM	mg/dl	0.026	38.7
Citrate	μM	mg/dl	52.1	0.020
Cortisol	nM	μg/dl	27.6	0.360
C-peptide	nM	ng/ml	0.331	3.02
Creatinine	μM	mg/dl	88.4	0.011
Creatinine clearance	ml/s	ml/min	0.017	60.0
Cyclic adenosine monophosphate	nmol/mmol creatinine	mol/g creatinine	113	0.009
Epinephrine	pM	pg/ml	5.46	0.183
Estrogen	pM	pg/ml	3.67	0.273
Fatty acids, nonesterified	g/L	mg/dl	0.01	100
Fructose	mM	mg/dl	0.056	18.0
Galactose (children)	mM	mg/dl	0.056	18.0
Gastrin	ng/L	pg/ml	1.00	1.00
Gastrointestinal polypeptide	pM	pg/ml	0.201	4.98
Glucagon	ng/L	pg/ml	1.00	1.00
Glucose	mM	mg/dl	0.056	18.0
Glycerol (free)	mM	mg/dl	0.109	9.21
Growth hormone	μg/L	ng/ml	1.00	1.00
Hydroxybutyrate	μM	mg/dl	96.1	0.010
Hydroxyproline	$\mu mol \cdot day^{-1} \cdot m^{-2}$	$mg \cdot day^{-1} \cdot m^{-2}$	7.63	0.131
Insulin	pM	μU/ml	6.00	0.167
Lactate (as lactic acid)	mM	meq/L	1.00	1.00
Lipase	U/L	U/L	1.00	1.00
Lipoproteins	mM	mg/dl	0.026	38.7
Norepinephrine (radioenzymatic procedure)	nM	pg/ml	0.006	169
Osmolality	mmol/kg	mosmol/kg	1.00	1.00
Pancreatic polypeptide	pM	pg/ml	0.239	4.18
Phosphate (as inorganic phosphorus)	mM	mg/dl	0.323	3.10
Phospholipid phosphorus, total	mM	mg/dl	0.323	3.10
Phospholipids, substance fraction of total phospholipid				
Lysophosphatidalcholine	Express as decimal	% of total	0.010	100
Phosphatidylcholine	Express as decimal	% of total	0.010	100
Phosphatidylethanolamine	Express as decimal	% of total	0.010	100
Sphingomyelin	Express as decimal	% of total	0.010	100
Potassium	mM	meq/L	1.00	1.00
Prolactin	μg/L	ng/ml	1.00	1.00
Protein, total	g/L	g/dl	10.0	0.100
Pyruvate (as pyruvic acid)	M	mg/dl	114	0.009
Renin	$ng \cdot L^{-1} \cdot s^{-1}$	$ng \cdot ml^{-1} \cdot h^{-1}$	0.278	3.60
Somatostatin	pM	pg/ml	0.611	1.64
Steroids				
Hydroxycorticosteroids (as cortisol)	μmol/day	mg/day	2.76	0.363
17-Ketogenic steroids (as dehydroepiandrosterone)	μmol/day	mg/day	3.47	0.288
17-Ketosteroids (as dehydroepiandrosterone)	μmol/day	mg/day	3.47	0.288
Ketosteroid fractions				
Androsterone	μmol/day	mg/day	3.44	0.290
Dehydroepiandrosterone	μmol/day	mg/day	3.47	0.288
Etiocholanolone	μmol/day	mg/day	3.44	0.290
Thyroxine	nM	μg/dl	12.9	0.078
TSH (thyroid-stimulating hormone)	mU/L	μU/ml	1.00	1.00
Urea nitrogen	mM	mg/dl	0.357	2.8
Vasoactive intestinal polypeptide	pM	pg/ml	0.331	3.02

Practical Diabetes Information...



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Diaβeta® TABLETS 1.25, 2.5 & 5mg

GLYBURIDE HOECHST-ROUSSEL

FOR EFFECTIVE CONTROL OF TYPE II DIABETES

Brief Summary

DIABETA® (glyburide) Tablets

CONTRAINDICATIONS: DIABETA® 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.

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

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

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

PRECAUTIONS: General — *Hypoglycemia:* All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection and dosage and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may increase the risk of serious hypoglycemic reactions. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency, are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used. *Loss of Control of Blood Glucose:* In diabetic patients exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. It may then be necessary to discontinue DIABETA® and administer insulin. *Information for Patients:* Patients should be informed of the potential risks and advantages of DIABETA® and of alternative modes of therapy. They also should be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained. **Laboratory Tests:** Response to DIABETA® Tablets should be monitored by frequent urine glucose tests and periodic blood glucose tests. Measurement of glycosylated hemoglobin levels may be helpful in some patients. **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. Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Studies in rats at doses up to 300 mg/kg/d for 18 months showed no carcinogenic effects. Glyburide is nonmutagenic when studied in Salmonella microsome test (Ames test) and in the DNA damage/alkaline elution assay. **Pregnancy:** *Teratogenic Effects:* Pregnancy Category B. Reproduction studies in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus due to glyburide. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Insulin should be used during pregnancy to maintain blood glucose 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. DIABETA® should be discontinued at least two weeks before the expected delivery date. **Nursing Mothers:** Some sulfonylurea drugs are known to be excreted in human milk. If DIABETA® is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered. **Pediatric Use:** Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Hypoglycemia: See Precautions and Overdosage sections. **Gastrointestinal Reactions:** Cholestatic jaundice and hepatitis may occur rarely, DIABETA® Tablets should be discontinued if this occurs. Gastrointestinal disturbances, eg, nausea, epigastric fullness, and heartburn, are the most common reactions, having occurred in 1.8% of treated patients during clinical trials. They tend to be dose-related and may disappear when dosage is reduced. Liver function abnormalities, including isolated transaminase elevations, have been reported. **Dermatologic Reactions:** Allergic skin reactions, eg, pruritis, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in 1.5% of treated patients. These may be transient and may disappear despite continued use of DIABETA®; 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 and disulfiram-like reactions have been reported with sulfonylureas; however, hepatic porphyria has not been reported with DIABETA® and disulfiram-like reactions have been reported very rarely. Cases of hyponatremia have been reported with glyburide 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.

OVERDOSAGE: Overdosage of sulfonylureas, including DIABETA® Tablets, can produce hypoglycemia. 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 which 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. Q69417-191

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With chronic administration in type II diabetic patients, the blood glucose-lowering effect of DiaBeta® persists despite a gradual decline in the insulin secretory response to the drug. Although the mechanism by which DiaBeta® lowers blood glucose has not been clearly established, there is evidence to suggest that excellent glycemic control without sustained high levels of insulin can be achieved because, among other possible mechanisms, glyburide appears to reduce hepatic glucose production and to enhance tissue uptake of glucose.[1–4]

All sulfonylureas, including DiaBeta,® can cause severe hypoglycemia.

References: 1. Feldman JM, Lebovitz HE. Endocrine and metabolic effects of glybenclamide — evidence for an extrapancreatic mechanism of action. *Diabetes* 1971;20:745–755. 2. Simonson DC, Ferrannini E, Bevilacqua S, et al. Mechanism of improvement in glucose metabolism after chronic glyburide therapy. *Diabetes* 1984;33:838–845. 3. Jaber LA, Wenzloff NJ, Komanicky P, Antal EJ. An evaluation of the therapeutic effects and dosage equivalence of glyburide and glipizide. *J Clin Pharmacol* 1990;30(2):181–188. 4. Shapiro ET, Van Cauter E, Tillil H, et al. Glyburide enhances the responsiveness of the β-cell to glucose, but does not correct the abnormal patterns of insulin secretion in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1989;69:571–576.

DiaBeta® TABLETS 1.25, 2.5 & 5 mg
GLYBURIDE HOECHST-ROUSSEL

Please see adjacent page for brief summary of prescribing information.

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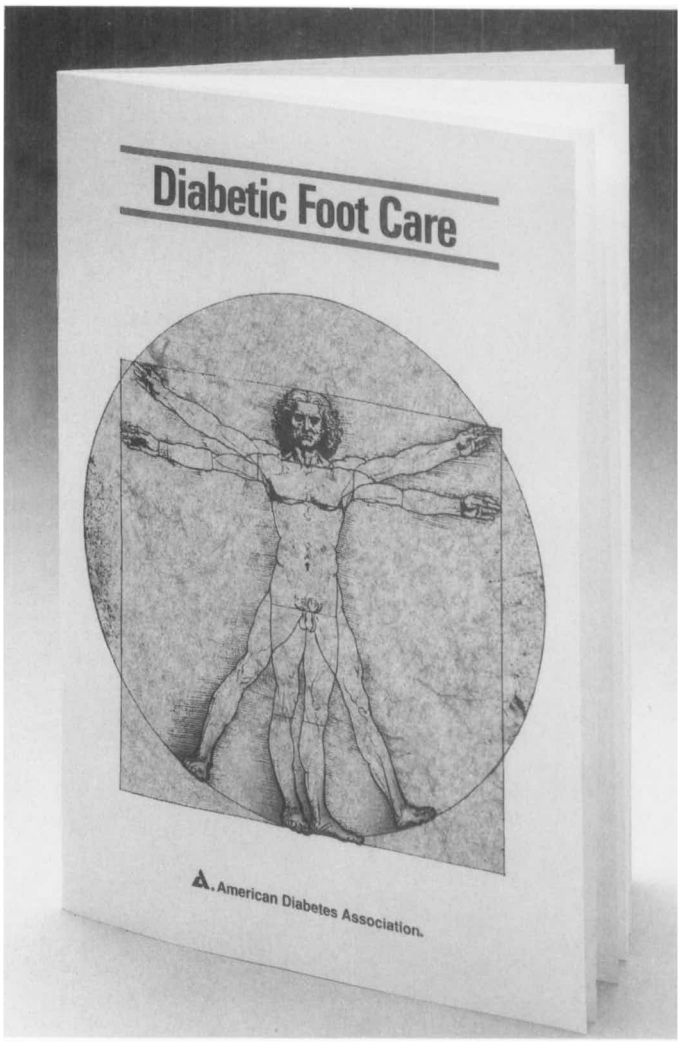

Diabetic foot problems are a major chronic complication of diabetes. As a concerned health-care professional who cares for people with diabetes, educating your patients on proper foot care and routinely evaluating the condition of their feet is an important and critical responsibility. You can have a direct impact on the incidence of infection that can lead to the tragedy of amputation.

Diabetic Foot Care, guidelines prepared by the Council on Foot Care of the American Diabetes Association, discusses the following issues:

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- Treatment of diabetic foot ulcers
- Criteria for therapeutic shoe design
- Diagnosis of neuroarthropathic joints
- Patient instructions for diabetic foot care

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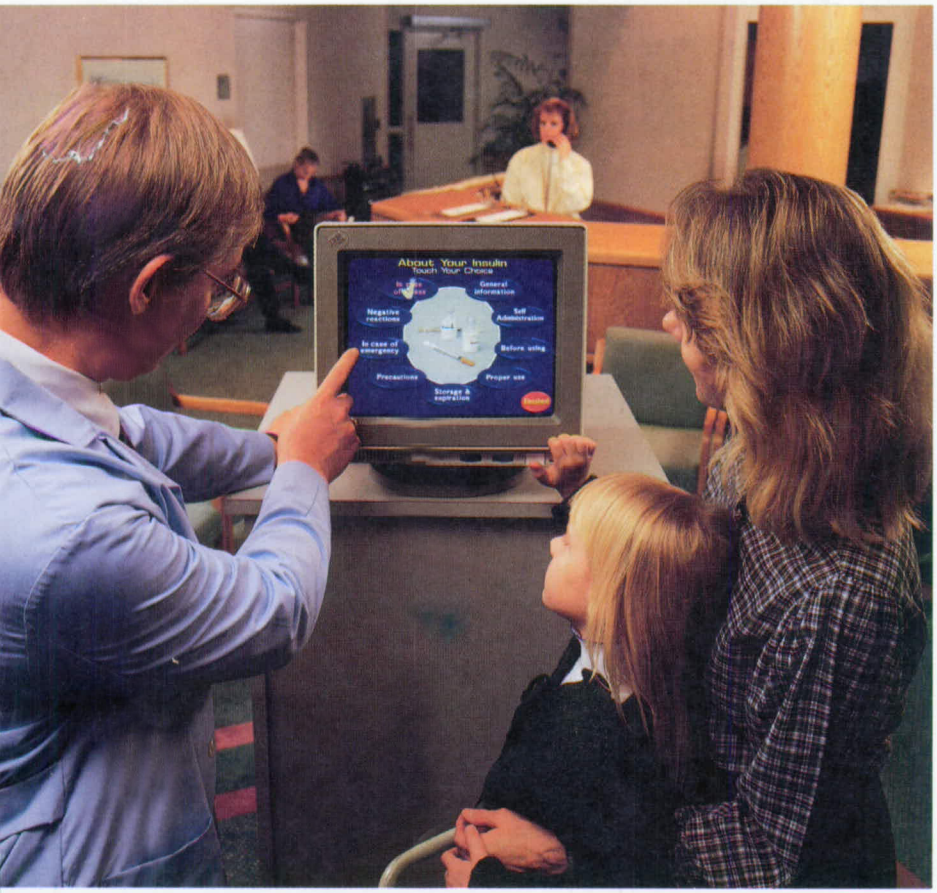
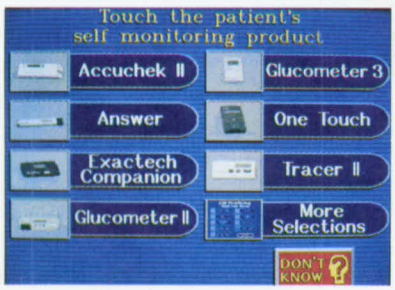
INTRODUCING
A Comprehensive Patient Education System



Touch screen technology makes learning easy and interesting for patients of all ages.

> *"We have found that this program is consistent with our teaching protocols. And, it's a wonderful experience when an educator can present material in a way that excites the patient."*
>
> Kitty Dobberstein, Director of Patient Education, Grady Memorial Hospital, Atlanta, GA



Specific monitoring devices are demonstrated.

System features full motion video.

The American Diabetes Association (ADA) recognizes diabetes education as one of the most important aspects of a comprehensive diabetes treatment program. That's why the ADA has joined forces with U.S. Pharmacopeia (USP) to develop an interactive video system for diabetes patient education. USP is a leading provider of drug and patient education information.

Reduces Learning Time

To improve the effectiveness of any diabetes treatment plan, patients must learn a significant amount of new information in a short period of time. Studies show that interactive technologies, like USP DI Visualized™ - *About Your Diabetes*,™ can reduce learning time requirements by an average of fifty percent.

With *About Your Diabetes* learning is fun—which means patients of all ages will be more likely to pay attention. And *About Your Diabetes* lets health care professionals make sure that the patient understands the information presented.

Easy to Use for Patients of All Ages

About Your Diabetes combines full-motion video, colorful graphics, and helpful narration with touch screen technology to provide an education system which encourages full patient involvement.

Developed in Conjunction with the ADA

About Your Diabetes was developed jointly by the American Diabetes Association and the U.S. Pharmacopeia, combining two databases of diabetes information into one comprehensive system.

For more information on how you can provide this interactive education system for your patients, contact:

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A Comprehensive Patient Education System

American Diabetes Association®

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If you need specific information not available here, call our toll-free number 1-800-232-3472.

Please send completed application with your dues payment to: American Diabetes Association, Professional Section Membership, 1660 Duke Street, Alexandria, VA 22314

JUPM031

ONCE-DAILY

ZESTRIL®!

LISINOPRIL-STUART

sustained BP control over 24 hours*

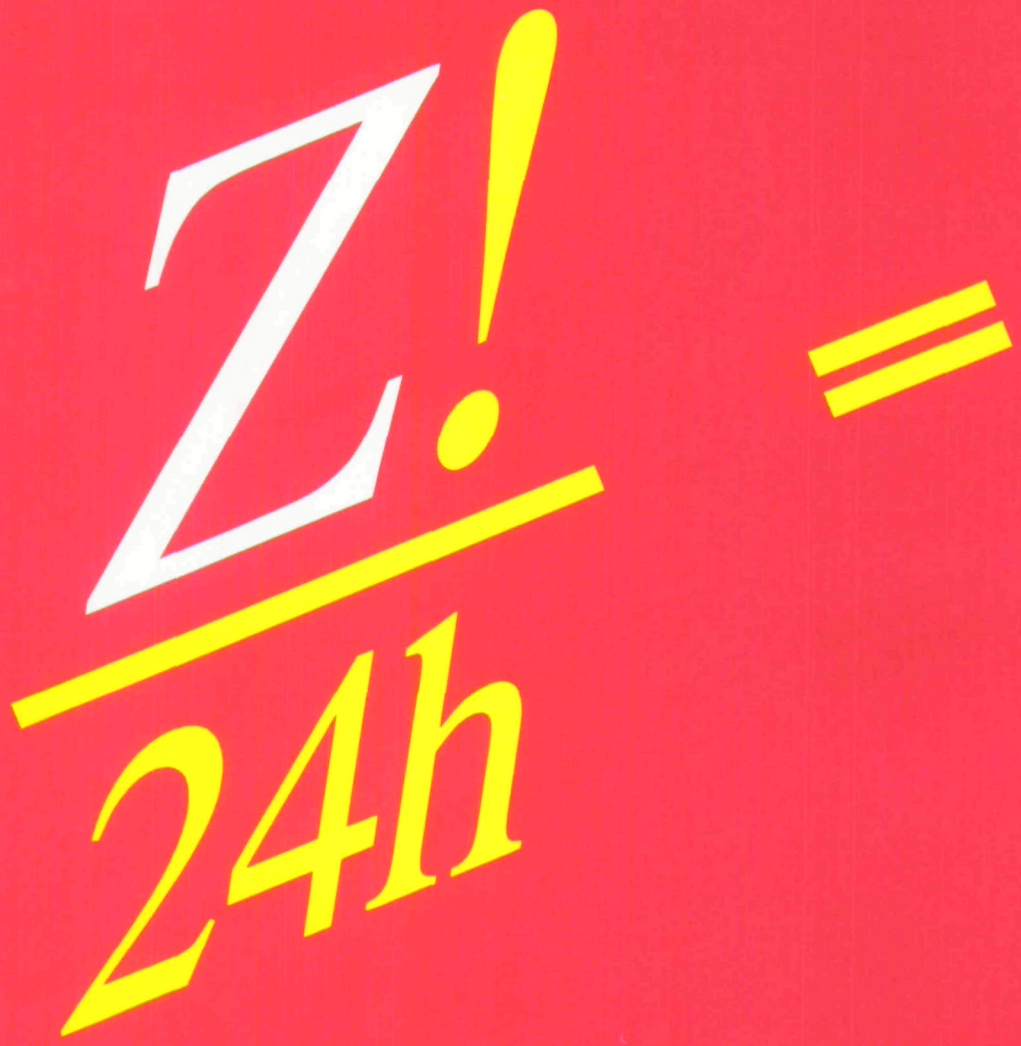
* The antihypertensive effect may diminish at the end of the dosing interval.

Please see last page of this advertisement for brief summary of prescribing information.

ONCE-DAILY

ZESTRIL®!

LISINOPRIL-STUART



*The antihypertensive effect may diminish at the end of the dosing interval.

†Multicenter, double-blind study involving 70 patients with mild-to-moderate hypertension (baseline office diastolic blood pressure [BP] ≥ 95 mm Hg and ≤ 114 mm Hg) in which BP assessments were made in the office as the primary efficacy endpoint, and by 24-hour ambulatory BP monitoring. Once-daily ZESTRIL and twice-daily captopril were titrated every 2 weeks according to whether office diastolic BP achieved a reduction to < 90 mm Hg or ≥ 10 mm Hg from baseline. If such a reduction occurred after 2 weeks on a dose, a patient remained on that dose to the end of treatment for 2 additional weeks. If a patient did not achieve such a reduction on any of the 3 study doses, treatment was ended after 2 weeks on the maximum dose.

‡24-hour ambulatory BP measurements were performed at pretreatment baseline and at the end of treatment for all randomized patients.

§**The long-term prognostic significance of blood pressure control determined by ambulatory BP monitoring has yet to be confirmed.**

Please see last page of this advertisement for brief summary of prescribing information.

*sustained BP control**

Results of a 4-8 week course of treatment in a multicenter study[†]

OFFICE BP MEASUREMENTS

Once-daily ZESTRIL equal to b.i.d. captopril in reducing BP, comparing baseline to end of treatment[1]

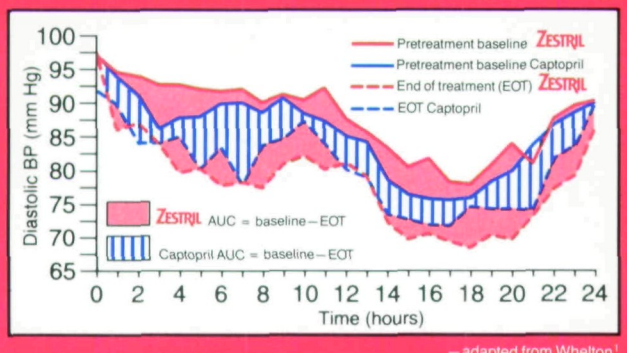
BP reductions from baseline as measured in the office showed no significant difference at $P < .05$ between once-daily ZESTRIL and twice-daily captopril[1]

AMBULATORY BP MEASUREMENTS[‡]

Once-daily ZESTRIL reduced BP better than b.i.d. captopril, comparing baseline to end of treatment[1]

BP reductions from baseline as measured by 24-hour ambulatory BP monitoring[§] showed that once-daily ZESTRIL tablets 10-40 mg reduced BP better than b.i.d. captopril 25-100 mg, with statistically significant ($P < .05$) differences in both systolic and diastolic area under the curve (AUC) measurements[1]

Ambulatory BP measurements (diastolic): Pretreatment baseline vs end of treatment (4-8 weeks)[1]



—adapted from Whelton[1]

The graph is based on the ambulatory diastolic blood pressure readings available for 32 ZESTRIL patients and 29 captopril patients with readings taken both before and at the end of the treatment period. At the time of their end-of-treatment readings, these patients had received 4 weeks of therapy, except as otherwise noted, at the following dosages: ZESTRIL patients: 19 (10 mg q.d.), 10 (20 mg q.d.), 1 (40 mg q.d.), and 2 (40 mg q.d.—2 weeks); captopril patients: 17 (25 mg b.i.d.), 5 (50 mg b.i.d.), 3 (100 mg b.i.d.), and 4 (100 mg b.i.d.—2 weeks).

ONCE-DAILY ZESTRIL®!
LISINOPRIL · STUART

ONCE-DAILY

ZESTRIL®!

LISINOPRIL-STUART

- ZESTRIL, like other ACE inhibitors, is well tolerated and has a low incidence of side effects
- ZESTRIL provides patient convenience with once-daily dosing* without regard to meals

ZESTRIL and other ACE inhibitors[2-6]

	Dosing* frequency (tablets)	Can be taken without regard to meals	Absorbed as the active drug
ONCE-DAILY ZESTRIL! LISINOPRIL-STUART [2]	●	[3]	
Enalapril [4]	●/●●		
Captopril [5]	●●/●●●	[6]	

Evaluation of the hypertensive patient should always include assessment of renal function (see Dosage and Administration).

Angioedema has been reported with ACE inhibitors, including ZESTRIL (see Warnings).

*The antihypertensive effect may diminish at the end of the dosing interval.

Z!/24h

REFERENCES: **1.** Whelton A, Miller WE, Dunne B Jr, Hait HI, Tresznewsky ON. Once-daily lisinopril compared with twice-daily captopril in the treatment of mild to moderate hypertension: assessment of office and ambulatory blood pressures. *J Clin Pharmacol.* 1990;30:1074-1080. **2.** *Physicians' Desk Reference®*. 44th ed. Oradell, NJ: Medical Economics Co; 1990. Zestril® (lisinopril):2175-2178. **3.** Mojaverian P, Rocci ML Jr, Vlasses PH, Hoholick C, Clementi RA, Ferguson RK. Effect of food on the bioavailability of lisinopril, a nonsulfhydryl angiotensin-converting enzyme inhibitor. *J Pharm Sci.* 1986;75:395-397. **4.** *Physicians' Desk Reference®*. 44th ed. Oradell, NJ: Medical Economics Co; 1990: Vasotec® (enalapril maleate, MSD): 1461-1464. **5.** *Physicians' Desk Reference®*. 44th ed. Oradell, NJ: Medical Economics Co; 1990; Capoten® (captopril): 2129-2132. **6.** Heel RC, Brogden RN, Speight TM, Avery GS. Captopril: a preliminary review of its pharmacological properties and therapeutic efficacy. *Drugs.* 1980;20:409-452.

STUART PHARMACEUTICALS
A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA

ZESTRIL® (LISINOPRIL)

(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT.)

INDICATIONS AND USAGE: ZESTRIL is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents.

In using ZESTRIL, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that ZESTRIL does not have a similar risk. (See WARNINGS.)

CONTRAINDICATIONS: ZESTRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor.

WARNINGS: Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including ZESTRIL. In such cases, ZESTRIL should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx likely to cause airway obstruction, appropriate therapy, eg, subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway should be promptly provided. (See ADVERSE REACTIONS.)**

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of the use with ZESTRIL in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of ZESTRIL and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of ZESTRIL are insufficient to show that ZESTRIL does not cause agranulocytosis at similar rates. Marketing experience has revealed rare cases of neutropenia and bone marrow depression in which a causal relationship to lisinopril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors, including ZESTRIL, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

Lisinopril crosses the human placenta. When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and/or death in the newborn. Oligohydramnios has also been reported, presumably representing decreased renal function in the fetus; limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation have been reported in association with oligohydramnios. Patients who do require ACE inhibitors during the second and third trimesters of pregnancy should be apprised of the potential hazards to the fetus, and frequent ultrasound examinations should be performed to look for oligohydramnios. If oligohydramnios is observed, ZESTRIL should be discontinued unless it is considered life-saving for the mother.

Other potential risks to the fetus/neonate exposed to ACE inhibitors include: intrauterine growth retardation, prematurity, patent ductus arteriosus; fetal death has also been reported. It is not clear, however, whether these reported events are related to ACE inhibition or the underlying maternal disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

Infants exposed in utero to ACE inhibitors should be closely monitored for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion.

Another ACE inhibitor, enalapril, has been removed from the neonatal circulation by peritoneal dialysis and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure. There is no experience with either of these procedures for removing lisinopril or other ACE inhibitors from the neonatal circulation.

Lisinopril was not teratogenic in mice treated on days 6-15 of gestation with up to 1,000 mg/kg/day (625 times the maximum recommended human dose). There was an increase in fetal resorptions at doses down to 100 mg/kg; at doses of 1,000 mg/kg this was prevented by saline supplementation. There was no fetotoxicity or teratogenicity in rats treated with up to 300 mg/kg/day (188 times the maximum recommended dose) of lisinopril at days 6-17 of gestation. In rats receiving lisinopril from day 15 of gestation through day 21 postpartum, there was an increased incidence in pup deaths on days 2-7 postpartum and a lower average body weight of pups on day 21 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation.

Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to angiotensin converting enzyme inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man.

Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorptions at an oral dose of lisinopril of 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). A single intravenous dose of 15 mg/kg of lisinopril administered to pregnant rabbits on gestation days 16, 21, or 26 resulted in 88% to 100% fetal death.

If ZESTRIL is used during pregnancy or if the patient becomes pregnant while taking ZESTRIL, the patient should be apprised of the potential hazards to the fetus.

PRECAUTIONS: General: Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ZESTRIL, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ZESTRIL and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ZESTRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of ZESTRIL and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.0% of patients with congestive heart failure. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ZESTRIL. (See Drug Interactions.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ZESTRIL may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients: Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of ZESTRIL. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned to report light-headedness especially during the first few days of therapy. If actual syncope occurs, the patient should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ZESTRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

DRUG INTERACTIONS: Hypotension - Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ZESTRIL. The possibility of hypotensive effects with ZESTRIL can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ZESTRIL. If it is necessary to continue the diuretic, initiate therapy with ZESTRIL at a dose of 5 mg daily, and provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS, and DOSAGE AND ADMINISTRATION.) When a diuretic is added to the therapy of a patient receiving ZESTRIL, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic. (See DOSAGE AND ADMINISTRATION.)

Indomethacin: In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of ZESTRIL alone were compared to ZESTRIL given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant.

Other Agents: ZESTRIL has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No clinically important pharmacokinetic interactions occurred when ZESTRIL was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of ZESTRIL.

Agents Increasing Serum Potassium: ZESTRIL attenuates potassium loss caused by thiazide-type diuretics. Use of ZESTRIL with potassium-sparing diuretics (eg, spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium with drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was usually reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if ZESTRIL is administered concomitantly with lithium.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 times* the maximum recommended daily human dose) or when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose).

*Based on patient weight of 50 kg.

Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an in vitro alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an in vitro test in Chinese hamster ovary cells or in an in vivo study in mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril.

Pregnancy: Pregnancy Category D. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers: Milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZESTRIL is given to a nursing mother.

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

ADVERSE REACTIONS: ZESTRIL has been found to be generally well tolerated in controlled clinical trials involving 2003 patients and subjects.

The most frequent clinical adverse experiences in controlled trials with ZESTRIL were dizziness (6.3%), headache (5.3%), fatigue (3.3%), diarrhea (3.2%), upper respiratory symptoms (3.0%), and cough (2.9%), all of which were more frequent than in placebo-treated patients. For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range.

For adverse experiences which occurred in more than 1% of patients and subjects treated with ZESTRIL or ZESTRIL plus hydrochlorothiazide in controlled clinical trials, comparative incidence data are listed in the table below.

Percent of Patients in Controlled Studies

	ZESTRIL (n=2003†) Incidence (discontinuation)	ZESTRIL/ Hydrochlorothiazide (n=644) Incidence (discontinuation)	Placebo (n=207) Incidence
Dizziness	6.3 (0.6)	9.0 (0.9)	1.9
Headache	5.3 (0.2)	4.3 (0.5)	1.9
Fatigue	3.3 (0.2)	3.9 (0.5)	1.0
Diarrhea	3.2 (0.3)	2.6 (0.3)	2.4
Upper Respiratory Symptoms	3.0 (0.0)	4.5 (0.0)	0.0
Cough	2.9 (0.4)	4.5 (0.8)	1.0
Nausea	2.3 (0.3)	2.5 (0.2)	2.4
Hypotension	1.8 (0.8)	1.6 (0.5)	0.5
Rash	1.5 (0.4)	1.6 (0.2)	0.5
Orthostatic Effects	1.4 (0.0)	3.4 (0.2)	1.0
Asthenia	1.3 (0.4)	2.0 (0.2)	1.0
Chest Pain	1.3 (0.1)	1.2 (0.2)	1.4
Vomiting	1.3 (0.2)	1.4 (0.0)	0.5
Dyspnea	1.1 (0.0)	0.5 (0.2)	1.4
Dyspepsia	1.0 (0.0)	1.9 (0.0)	0.0
Paresthesia	0.8 (0.0)	2.0 (0.2)	0.0
Impotence	0.7 (0.2)	1.6 (0.3)	0.0
Muscle Cramps	0.6 (0.0)	2.8 (0.6)	0.5
Back Pain	0.5 (0.0)	1.1 (0.0)	1.4
Nasal Congestion	0.3 (0.0)	1.2 (0.0)	0.0
Decreased Libido	0.2 (0.1)	1.2 (0.0)	0.0
Vertigo	0.1 (0.0)	1.1 (0.2)	0.0

† Includes 420 patients treated for congestive heart failure who were receiving concomitant digitalis and/or diuretic therapy.

Clinical adverse experiences occurring in 0.3% to 1.0% of patients in the controlled trials and rarer, serious, possibly drug related events reported in uncontrolled studies or marketing experience are listed below and, within each category, are in order of decreasing severity.

BODY AS A WHOLE: Chest discomfort, fever, flushing, malaise.

CARDIOVASCULAR: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension); angina pectoris, orthostatic hypotension, rhythm disturbances, tachycardia, peripheral edema, vasculitis, palpitation.

DIGESTIVE: Pancreatitis, hepatitis (hepatocellular or cholestatic jaundice), abdominal pain, anorexia, constipation, flatulence, dry mouth.

METABOLISM: Gout

MUSCULOSKELETAL: Joint pain, shoulder pain.

NERVOUS SYSTEM/PSYCHIATRIC: Depression, somnolence, insomnia, stroke, nervousness, confusion.

RESPIRATORY SYSTEM: Bronchitis, sinusitis, pharyngeal pain.

SKIN: Urticaria, pruritus, diaphoresis.

SPECIAL SENSES: Blurred vision.

UROGENITAL: Oliguria, progressive azotemia, acute renal failure, urinary tract infection.

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia and fever.

ANGIOEDEMA: Angioedema has been reported in patients receiving ZESTRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with ZESTRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

HYPOTENSION: In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients. Hypotension or syncope was a cause of discontinuation of therapy in 0.5% of hypertensive patients. (See WARNINGS.)

In patients with congestive heart failure, hypotension occurred in 5.0% and syncope occurred in 1.0% of patients. These adverse experiences were causes for discontinuation of therapy in 1.3% of these patients.

Fetal/Neonatal Morbidity and Mortality: In infants exposed in utero to ACE inhibitors the following adverse experiences have been reported: Fetal and neonatal death, renal failure, hypoplastic lung development, hypotension, hyperkalemia, skull hypoplasia, limb contractures, craniofacial deformities, intrauterine growth retardation, prematurity and patent ductus arteriosus. (See WARNINGS, Fetal/Neonatal Morbidity and Mortality.)

Clinical Laboratory Test Findings: Serum Electrolytes: Hyperkalemia. (See PRECAUTIONS.)

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0% of patients with essential hypertension treated with ZESTRIL alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. (See PRECAUTIONS.) Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 9.1% of patients with congestive heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g% and 1.3 vol%, respectively) occurred frequently in patients treated with ZESTRIL but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. In marketing experience, rare cases of neutropenia and bone marrow depression have been reported.

Overall, 2.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%) and serum potassium (0.4%).

DOSAGE AND ADMINISTRATION: Initial Therapy: In patients with uncomplicated essential hypertension not on diuretic therapy, the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20-40 mg per day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. Doses up to 80 mg have been used but do not appear to give greater effect. If blood pressure is not controlled with ZESTRIL alone, a low dose of a diuretic may be added. Hydrochlorothiazide, 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of ZESTRIL.

Diuretic Treated Patients: In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of ZESTRIL. The diuretic should be discontinued, if possible, for two to three days before beginning therapy with ZESTRIL to reduce the likelihood of hypotension. (See WARNINGS.) The dosage of ZESTRIL should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with ZESTRIL alone, diuretic therapy may be resumed as described above.

If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.)

Concomitant administration of ZESTRIL with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. (See PRECAUTIONS.)

Use in Elderly: In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of ZESTRIL. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution.

Dosage Adjustment in Renal Impairment: The usual dose of ZESTRIL (10 mg) is recommended for patients with creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≥ 10 mL/min ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 5 mg once daily. For patients with creatinine clearance < 10 mL/min (usually on hemodialysis) the recommended initial dose is 2.5 mg. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Renal Status	Creatinine Clearance mL/min	Initial Dose mg/day
Normal Renal Function to Mild Impairment	>30	10
Moderate to Severe Impairment	≥10 ≤30	5
Dialysis Patients	<10	2.5‡

‡ Dosage or dosing interval should be adjusted depending on the blood pressure response.

HOW SUPPLIED

5 mg Tablets (NDC 0038-0130) pink, round, biconvex, uncoated, scored tablets, identified "ZESTRIL 5" debossed on one side, and "130" debossed and scored on the other side are supplied in bottles of 100 tablets and unit dose packages of 100 tablets.

10 mg Tablets (NDC 0038-0131) pink, round, biconvex, uncoated tablets identified "ZESTRIL 10" debossed on one side, and "131" debossed on the other side are supplied in bottles of 100 tablets and unit dose packages of 100 tablets.

20 mg Tablets (NDC 0038-0132) red, round, biconvex, uncoated tablets identified "ZESTRIL 20" debossed on one side, and "132" debossed on the other side are supplied in bottles of 100 tablets and unit dose packages of 100 tablets.

40 mg Tablets (NDC 0038-0134) yellow, round, biconvex, uncoated tablets identified "ZESTRIL 40" debossed on one side, and "134" debossed on the other side are supplied in bottles of 100 tablets and unit dose packages of 100 tablets.

Store at room temperature. Protect from moisture, freezing and excessive heat. Dispense in a tight container.

Rev V 01/91

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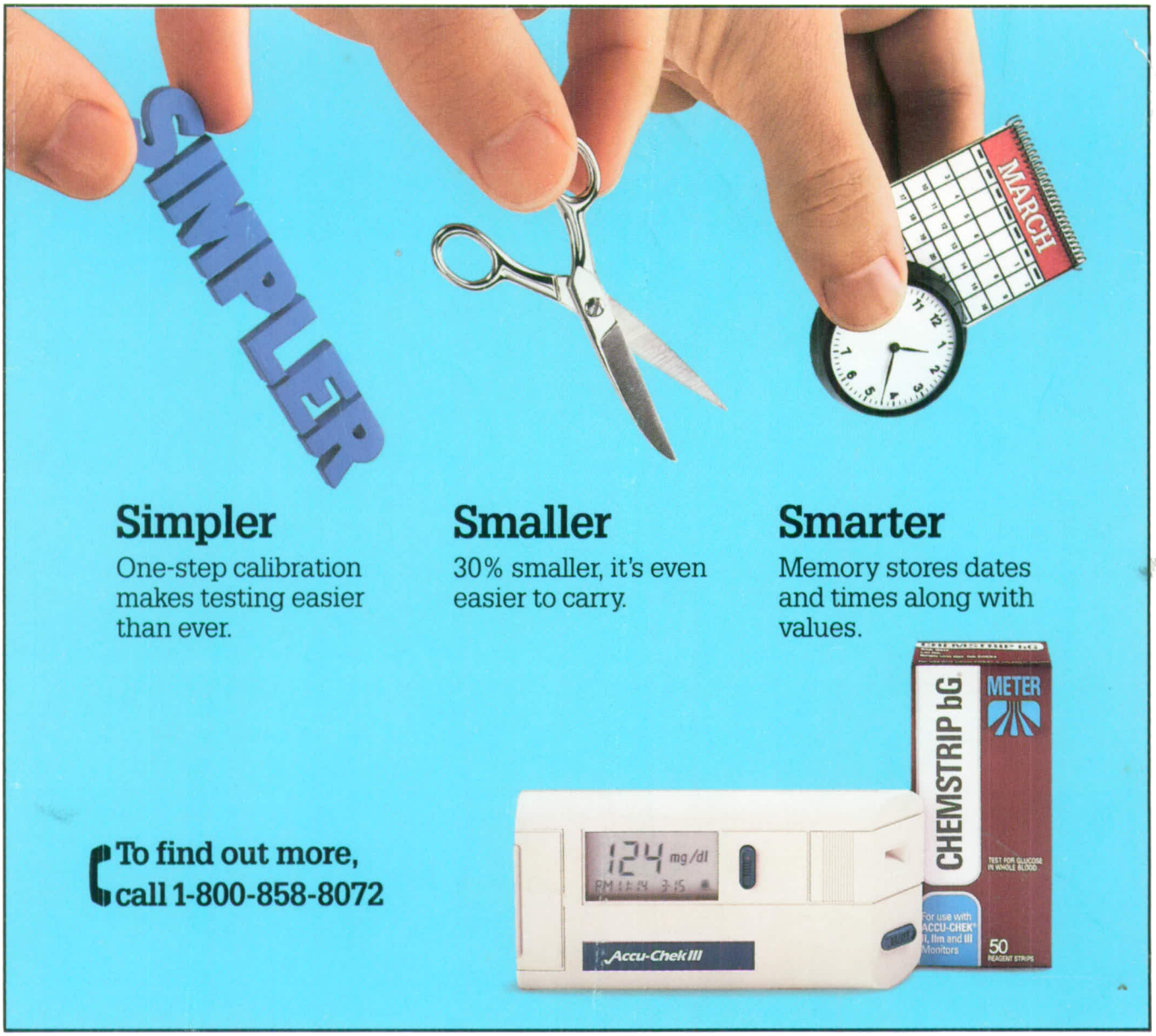

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