INFORMATION FOR AUTHORS

These guidelines are in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals." (The complete document is available in the June 12, 1982, issue of the *British Medical Journal* and the June 1982 issue of the *Annals of Internal Medicine.)*

MANUSCRIPTS

Manuscripts containing original material are accepted for consideration with the understanding that neither the article nor any part of its essential substance, tables, or figures has been or will be published or submitted for publication elsewhere before appearing in the *Journal.* This restriction does not apply to abstracts or press reports published in connection with scientific meetings. Copies of any possibly duplicative manuscripts should be submitted to the Editor along with the manuscript that is to be considered by the *Journal.* The *Journal* strongly discourages the submission of more than one article dealing with related aspects of the same study. In almost all cases, a single study is best reported in a single paper.

Submit an original and one copy of the complete manuscript, including text pages, legends, tables, references, and glossy prints of figures. Only typed copy, on standard-sized typewriter paper and double-spaced throughout, with margins of at least 2.5 cm, is acceptable. Address all submissions to John P. Geyman, M.D., Editor, the *Journal of the American Board of Family Practice,* Dept. of Family Medicine (RF-30), School of Medicine, University of Washington, Seattle, WA 98195. A covering letter should identify the person (with the address and telephone number) responsible for negotiations concerning the manuscript; the letter should make it clear that the final manuscript has been seen and approved by all authors.

CONFLICT OF INTEREST

The *Journal* expects authors to disclose any commercial associations that might pose a conflict of interest in connection with the submitted article. All funding sources supporting the work should be routinely acknowledged on the title page, as should all institutional or corporate affiliations of the authors. Other kinds of associations, such as consultancies, stock ownership or other equity interests, or patent-licensing arrangements, should be disclosed to the Editor in a covering letter at the time of submission. Such information will be held in confidence while the paper is under review and will not influence the editorial decision. If the manuscript is accepted, the Editor will discuss with the authors how best to disclose the relevant information. Questions about this policy should be directed to the Editor.

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The *Journal* will print measurements in Système International (SI) and conventional units (this practice applies only to clinical investigation and review articles). Authors may use either as their principal system; however, they must also provide the alternative numbers and units in parentheses.

TITLES AND AUTHORS' NAMES

With the manuscript, provide a page giving the title of the paper; a running head of fewer than 40 letter spaces; the name(s) of the author(s), including the first name(s) and academic degree(s); the name of the department and institution in which the work was done; and the name and address of the author to whom reprint requests should be addressed. Any grant support that requires acknowledgment should be mentioned on this page.

ABSTRACTS

Use another page to provide an abstract of not more than 175 words. This abstract should be factual, not descriptive, and should present the reason for the study, the main findings (give specific data if possible), and the principal conclusions.

KEY WORDS

The *Journal* has a policy of requiring authors to submit two to four key words with their manuscripts, to be used for purposes of classification by subject.

REFERENCES

References must be typed in double spacing and numbered consecutively as they are cited. References first cited in tables or figure legends must be numbered so that they will be in sequence with references cited in the text. The style of references is that of the *Index Medicus.* List all authors when there are six or fewer; when there are seven or more, list the first three, then "et al." Sample references are as follows:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide. N Engl J Med 1979; 301:1382-5.
2. Bearn AG. Wilson's disease. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, eds. The metabolic basis of inherited disease. New York: McGraw-Hill, 1972:1033-50.
3. Pellegrin FA, Ramcharan S, Fisch IR, Phillips NR. The noncontraceptive effects of oral contraceptive drugs: the Kaiser-Permanente Study. In: Ramcharan S, ed. The Walnut Creek Contraceptive Drug Study: a prospective study of the side effects of oral contraceptives. Vol. 1. Bethesda, Md.: National Institutes of Health, 1974:1-19. (DHEW publication no. (NIH)74-562).

Numbered references to personal communications, unpublished data, and manuscripts either "in preparation" or "submitted for publication" are unacceptable (see "Permissions"). If essential, such material may be incorporated in the appropriate place in the text.

TABLES

Type tables in double spacing on separate sheets, and provide a legend for each. Excessive tabular data are discouraged. If an article is accepted, the *Journal* will arrange to deposit extensive tables of important data with the National Auxiliary Publications Service (NAPS); we will pay for the deposit and add an appropriate footnote to the text. This service makes microfiche or photocopies of tables available at moderate charges to those who request them.

ILLUSTRATIONS

Figures should be professionally designed. Glossy, black-and-white photographs are requested. Symbols, lettering, and numbering should be clear, and these elements should be large enough to remain legible after the figure has been reduced to fit the width of a single column.

The back of each figure should include the sequence number, the name of the author, and the proper orientation (e.g., "top"). Do not mount the figure on cardboard. Photomicrographs should be cropped to a width of 8 cm, and electron photomicrographs should have internal scale markers.

If photographs of patients are used, either the subjects should not be identifiable or their pictures must be accompanied by written permission to use the figure. Permission forms are available from the Editor.

Legends for illustrations should be typewritten (double-spaced) on a separate sheet, and should not appear on the illustrations.

Color illustrations are used from time to time. Send both transparencies and prints for this purpose.

ABBREVIATIONS

Except for units of measurement, abbreviations are discouraged. Consult the *Council of Biology Editors Style Manual* (Fifth edition. Bethesda, Md.: Council of Biology Editors, 1983) for lists of standard abbreviations. The first time an abbreviation appears it should be preceded by the words for which it stands.

DRUG NAMES

Generic names should, in general, be used. If an author so desires, brand names may be inserted in parentheses.

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Sex bias should be avoided and gender-inclusive language used whenever possible.

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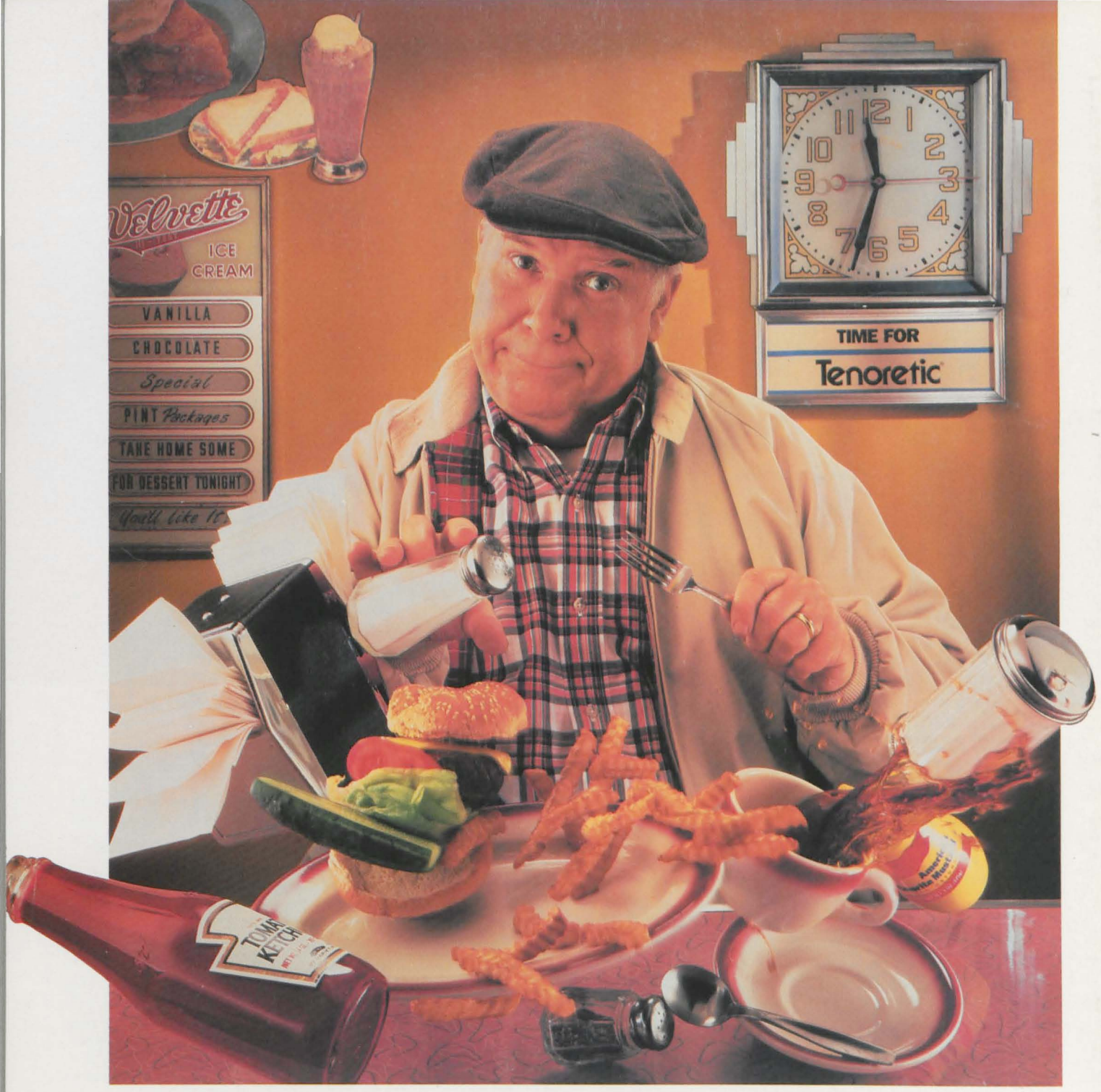
Manuscripts are examined by the editorial staff and are usually sent to outside reviewers. Authors will remain anonymous to outside reviewers and vice versa. External statistical review will be accomplished where appropriate.



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Mixed hyperlipidemias—elevated cholesterol *and* triglycerides—are common among heart attack victims,[1] and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.[2]

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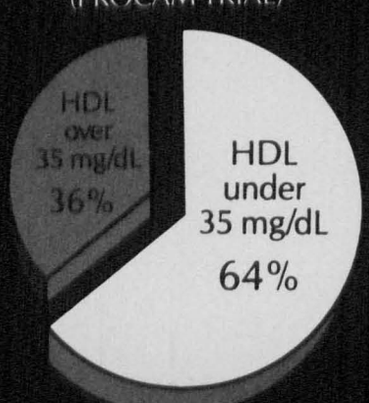

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*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973;52:1533-1543. **2.** Assmann G, Schulte H. *PROCAM-Trial: Prospective Cardiovascular Münster Trial.* Zürich: Panscientia Verlag; 1986:8-9. **3.** Data on file, Medical Affairs Dept, Parke-Davis **4.** Tikkanen MJ, Helve E, Jäättelä A, et al. Comparison between lovastatin and gemfibrozil in the treatment of primary hypercholesterolemia: the Finnish Multicenter Study. *Am J Cardiol.* 1988;62:35J-43J.

Please see last page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

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Before prescribing, please see full prescribing information.
A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

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from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B** – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers** – Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children** – Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

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CHAIR, DEPARTMENT OF FAMILY AND COMMUNITY MEDICINE

The Search Committee for the position of Chair of the Department of Family and Community Medicine, College of Medicine, invites applications and nominations for this position. The Chair will report to the Senior Vice President for Health Affairs and Dean and will be responsible for all administrative, academic and clinical activities of the department. The Department is in an expansion mode in response to Pennsylvania State University's commitment to family practice. In addition to the pre-doctoral program at The College of Medicine, the Department has a University Hospital/Community Hospital residency program and is expanding its teaching base into the community.

The following criteria will be used to aid in selecting a Chair of the Department of Family and Community Medicine. The candidate must demonstrate:

- Clinical excellence and accomplishment in the field of Family and Community Medicine.
- Administrative and leadership capabilities.
- Commitment to teaching and academic excellence.

The closing date for applications is November 15, 1990.

Nominations and letters of application should be sent to:

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This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.

Dyazide may be used alone or as an adjunct to other antihypertensive drugs; dosage adjustments may be necessary.

Contraindications: *Concomitant use with other potassium-sparing agents such as spironolactone or amiloride; potassium supplements (except in presence of severe hypokalemia); anuria, acute and chronic renal insufficiencies or significant renal impairment; hypersensitivity to drug or other sulfonamide-derived drugs; preexisting elevated serum potassium concentration.*

Warnings: *Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium-conserving diuretic combinations, including Dyazide. Hyperkalemia is more likely to occur in patients with renal impairment and diabetes (even without evidence of renal impairment), and in the elderly or severely ill. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving Dyazide, when dosages are changed or with any illness that may influence renal function.*

If hyperkalemia is suspected, obtain an ECG and monitor serum potassium. If hyperkalemia develops, discontinue Dyazide and initiate thiazide therapy if needed. Persistent hyperkalemia may require dialysis. Monitor serum electrolytes frequently in patients with mild renal dysfunction and in diabetic patients. In patients who may develop respiratory or metabolic acidosis, monitor serum electrolytes and acid/base balance frequently.

Precautions: *The bioavailability of the hydrochlorothiazide and triamterene components of Dyazide is about 50% of the maximum obtainable with oral therapy. Theoretically, a patient transferred from therapy with hydrochlorothiazide with or without triamterene might show an increase in blood pressure, fluid retention, or change in serum potassium. Extensive clinical experience with Dyazide, however, suggests that these conditions have not been commonly observed in clinical practice. (See CLINICAL PHARMACOLOGY.) Use thiazides cautiously in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease; potassium depletion induced by the thiazide may be important in this connection; administer Dyazide cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor; if mental confusion increases, discontinue Dyazide for a few days; attention must be given to other factors that may precipitate hepatic coma, such as blood in the gastrointestinal tract or preexisting potassium depletion. If patients develop hypokalemia, which is uncommon with Dyazide, increase potassium intake (i.e., with supplements or potassium-rich foods). If repeat determinations show serum potassium concentrations below 3.0 mEq/L, discontinue Dyazide and initiate potassium chloride supplementation. Institute corrective measures cautiously and monitor serum potassium concentrations frequently, especially in patients receiving digitalis or those with a history of cardiac arrhythmias. Diuretics may aggravate existing electrolyte imbalances, especially at high dosages or in patients on salt-restricted diets. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Chloride replacement may be required in the treatment of metabolic acidosis. If dilutional hyponatremia develops, restrict water intake. In actual salt depletion, initiate sodium chloride replacement. Use Dyazide cautiously in patients with a history of renal stone formation.*

If hyperkalemia develops when treating for hypokalemia, take corrective measures. Also discontinue Dyazide and, if appropriate, substitute a thiazide diuretic until potassium levels return to normal. Do periodic BUN and serum creatinine determinations, especially in the elderly and in patients with suspected or confirmed renal insufficiency. Serum PBI levels may decrease without signs of thyroid disturbance. Discontinue thiazides before conducting parathyroid function tests.

Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with Dyazide. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. A few occurrences of acute renal failure have been reported in patients on Dyazide when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with Dyazide. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine; therefore use cautiously in patients undergoing surgery. Monitor electrolytes in patients taking amphotericin B, corticosteroids or corticotropin concomitantly. Thiazides may potentiate the action of other antihypertensive drugs. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be needed. Dyazide may raise the level of blood uric acid; dosage adjustments of antigout medication may be needed to control hyperuricemia and gout. The following agents given with triamterene may promote serum potassium accumulation and possibly result in hyperkalemia, especially in patients with renal insufficiency: blood from blood bank (may contain up to 30 mEq of potassium per liter of plasma or up to 65 mEq of potassium per liter of whole blood when stored for more than 10 days); low-salt milk (may contain up to 60 mEq of potassium per liter); potassium-containing medications (such as parenteral penicillin G potassium), and salt substitutes (most contain substantial amounts of potassium). Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or rectally, reduce serum potassium concentrations by sodium replacement of the potassium; fluid retention may occur in some patients because of the increased sodium intake. Chronic or overuse of laxatives may reduce serum potassium concentrations by promoting excessive potassium loss from the intestinal tract; laxatives may interfere with the potassium-retaining effects of triamterene. The effectiveness of methenamine may be decreased when used concurrently with hydrochlorothiazide because of alkalinization of the urine. Dyazide will interfere with the fluorescent measurement of quinidine.

There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Thiazides and triamterene cross the placental barrier and appear in cord blood. The use of thiazides in pregnancy requires weighing the anticipated benefit against possible hazards, including fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. Thiazides appear, and triamterene may appear, in breast milk. If use of the drug is essential, the patient should stop nursing. Safety and effectiveness in children have not been established.

Adverse Reactions: *The serious adverse effects associated with Dyazide have commonly occurred in less than 0.1% of patients treated with this product. Anaphylaxis, rash, urticaria, photosensitivity, cardiac arrhythmias, postural hypotension, diabetes mellitus, hyperkalemia, hyperglycemia, glycosuria, hyperuricemia, hypokalemia, hyponatremia, acidosis, hypochloremia, jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and vomiting, diarrhea, constipation, abdominal pain, acute renal failure, interstitial nephritis, renal stones composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment, leukopenia, thrombocytopenia and purpura, megaloblastic anemia, muscle cramps, weakness, fatigue, dizziness, headache, dry mouth, impotence, sialadenitis. Thiazides alone have been shown to cause the following additional adverse reactions: paresthesias, vertigo, xanthopsia, transient blurred vision, allergic pneumonitis, pulmonary edema, respiratory distress, necrotizing vasculitis, exacerbation of lupus, aplastic anemia, agranulocytosis, hemolytic anemia. In neonates and infants: thrombocytopenia and pancreatitis—rarely, in newborns whose mothers have received thiazides during pregnancy.*

Supplied: *Capsules containing 25 mg hydrochlorothiazide and 50 mg triamterene, in bottles of 1000 capsules; in Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.*

BRS-DZ:L60

GRAY and BLACK:

Particularly Suited to the Red and White

DYAZIDE®

25 mg Hydrochlorothiazide/50 mg Triamterene/SKF

for hypertensives over 55 as well as black hypertensives

Before prescribing, please see brief summary of prescribing information on adjacent page.

SB

SmithKline Beecham

Pharmaceuticals

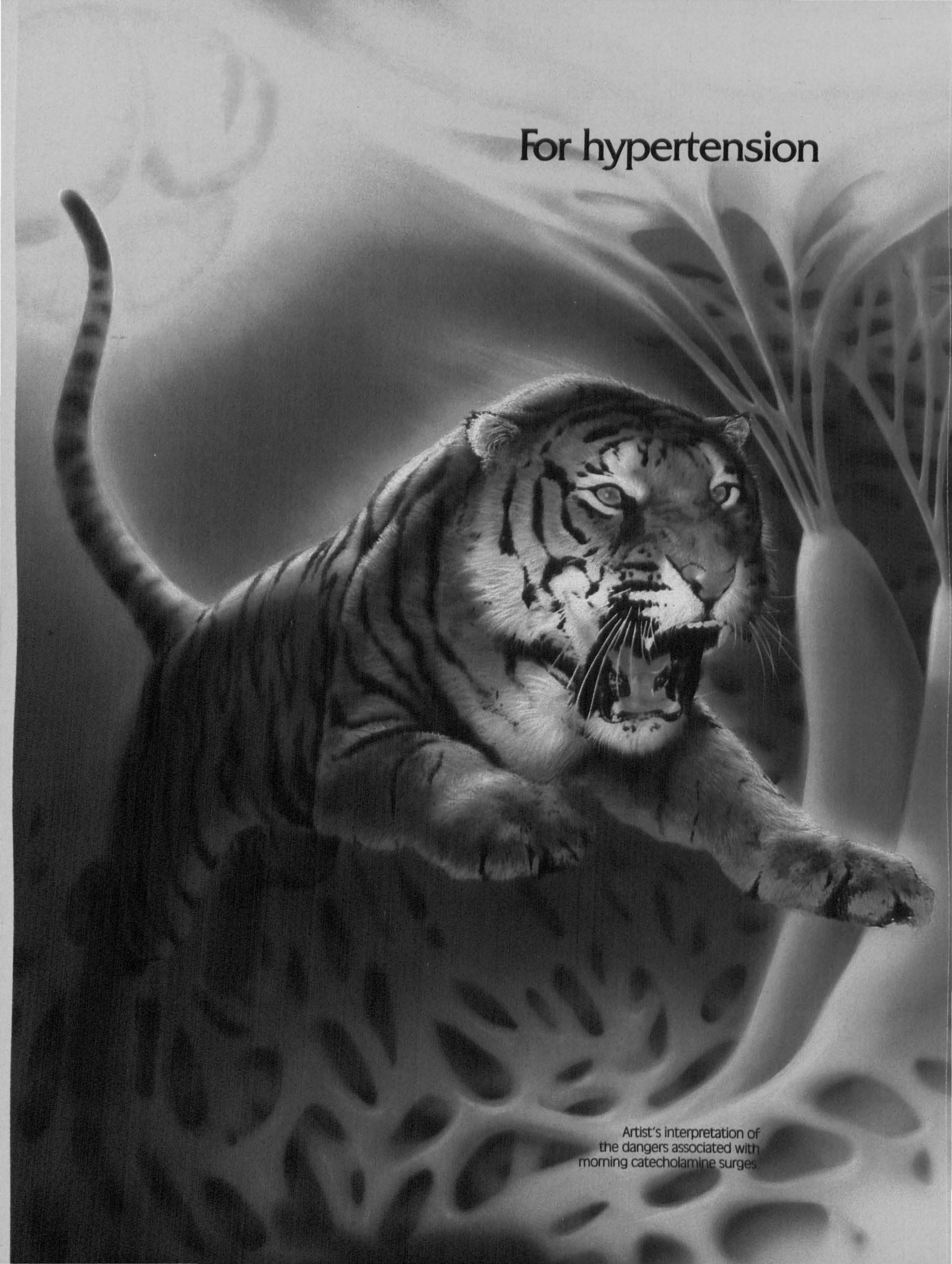
Catecholamines surge in the AM

IS TODAY'S WAKING HEART STILL PROTECTED BY YESTERDAY'S BETA-BLOCKER?

Introducing...

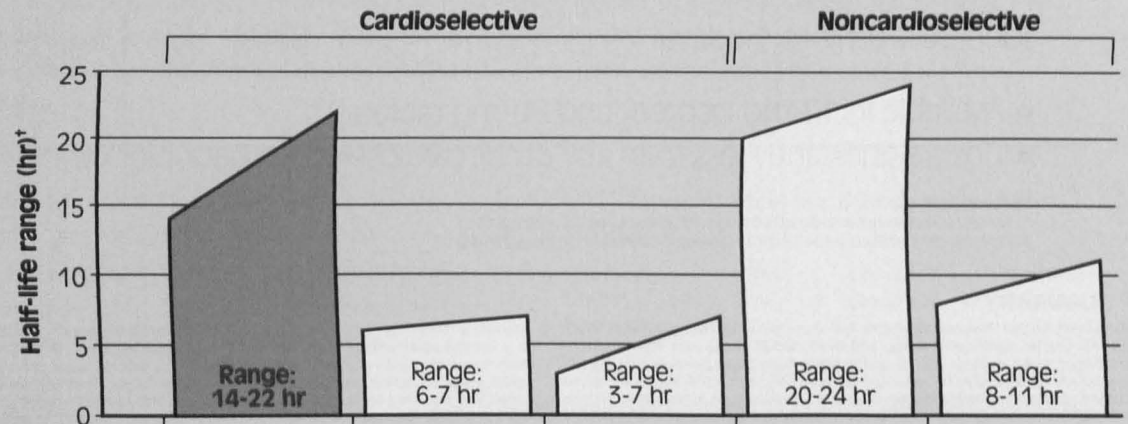
SEARLE

For hypertension



Artist's interpretation of
the dangers associated with
morning catecholamine surges.

24-HOUR BETA$_1$-BLOCKADE THAT'S STILL GOING STRONG WHEN THE "BIG CATS"* SURGE



	Kerlone® (betaxolol HCl)[1]	Tenormin® (atenolol)‡	Lopressor® (metoprolol)‡	Corgard® (nadolol)‡	Inderal® LA (propranolol HCl)§
Bioavailability†	89%	50%	50%	30%	9%-18%
Interpatient variations in plasma levels (n-fold)[2†]	2	4	10	7	NA

NA=not available in references cited.
† Numbers shown are not directly comparable since these data have been compiled from different study populations.
‡ Adapted from product information in *Physicians' Desk Reference®*, ed 44. Oradell, NJ, Medical Economics Co Inc, 1990.
§ *Drug Facts & Comparisons*. St Louis, Mo, JS Lippincott Co, 1990.

*Refers to catecholamines, norepinephrine and epinephrine, serum concentrations of which may increase two- to threefold in the morning compared with trough levels (Reference: Tofler GH, Brezinski D, Schafer AI, et al: Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden death. *N Engl J Med* 1987;316:1514-1518.)

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

Kerlone is contraindicated in patients with known hypersensitivity to betaxolol hydrochloride. As are other beta-blockers, Kerlone is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

Tenormin® is a registered trademark of ICI Pharma. Lopressor® is a registered trademark of Geigy Pharmaceuticals. Corgard® is a registered trademark of Princeton Pharmaceutical Company. Inderal® is a registered trademark of Wyeth-Ayerst Laboratories.

NEW β_1 Once-a-day **KERLONE®** *24 hours and still going strong*

(betaxolol HCl)

SEARLE

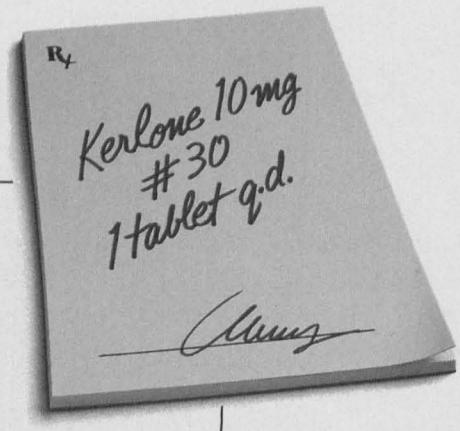
NEW

KERLONE®

β_1 Once-a-day

(betaxolol HCl)

24 hours and still going strong



10 mg

Usual initial dosage of Kerlone is 10 mg once a day. — In some patients, a 5-mg starting dose should be considered. Please see complete prescribing information.

If desired response is not achieved, dose may be doubled after 7 to 14 days.

- Available in 10-mg (scored) and 20-mg tablets
- Costs significantly less than any other cardioselective beta-blocker [2,3]

References:
1. Kerlone complete prescribing information. **2.** Data on file, G.D. Searle & Co.
3. *Drug Topics® Red Book*, ed 94. Oradell, N.J, Medical Economics Co Inc, April 1990.

BRIEF SUMMARY

Contraindications: Known hypersensitivity to the drug, sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see *Warnings*).

Warnings: In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, beta-blockers should be administered cautiously. At the first sign or symptom of cardiac failure, discontinuation of Kerlone should be considered. In some cases Kerlone can be continued while cardiac failure is treated with cardiac glycosides, diuretics, and other agents, as appropriate. Abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease has been followed by exacerbations of angina pectoris and, in some cases, myocardial infarction has been reported; patients should be warned against interruption of therapy without the physician's advice. When discontinuation of Kerlone is planned, the patient should be carefully observed and therapy should be reinstituted, at least temporarily, if withdrawal symptoms occur. **PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD NOT IN GENERAL RECEIVE BETA-BLOCKERS. Because of its relative β_1 selectivity, low doses of Kerlone may be used with caution in patients with bronchospastic disease who do not respond to or cannot tolerate alternative treatment. Since β_1 selectivity is not absolute and is inversely related to dose, the lowest possible dose of Kerlone should be used (5 to 10 mg once daily) and a bronchodilator should be made available. If dosage must be increased, divided dosage should be considered to avoid the higher peak blood levels associated with once-daily dosing.** The risk of excessive myocardial depression during general anesthesia may be increased and difficulty in restarting and maintaining the heart beat has been reported with beta-blockers. If treatment is continued, particular care should be taken when using anesthetic agents which depress the myocardium, and it is prudent to use the lowest possible dose of Kerlone. Beta-blockers should be used with caution in diabetic patients as they may mask tachycardia occurring with hypoglycemia (patients should be warned of this), although other manifestations such as dizziness and sweating may not be significantly affected. Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism. Abrupt withdrawal might precipitate a thyroid storm; therefore, patients known or suspected of being thyrotoxic from whom Kerlone is to be withdrawn should be monitored closely.

Precautions: Beta-adrenoceptor blockade can cause reduction of intraocular pressure. Since betaxolol hydrochloride is marketed as an ophthalmic solution for treatment of glaucoma, patients should be told that Kerlone may interfere with the glaucoma-screening test. Withdrawal may lead to a return of increased intraocular pressure. Patients receiving beta-adrenergic blocking agents orally and beta-blocking ophthalmic solutions should be observed for potential additive effects. Kerlone clearance is somewhat reduced in patients with renal failure but little changed in patients with hepatic disease. Dosage reductions have not routinely been necessary when hepatic and/or renal insufficiency is present but patients should be observed. Patients on dialysis require a reduced dose. Patients should be warned against interruption or discontinuation of Kerlone therapy without the physician's advice. Patients being treated with beta-adrenergic blocking agents should be advised to consult a physician at the first sign or symptom of cardiac failure. Patients should know how they react to this medicine before they operate automobiles and machinery or engage in other tasks requiring alertness; contact their physician if any difficulty in breathing occurs, and before surgery of any type; and inform their physicians or dentists that they are taking Kerlone. Patients with diabetes should be warned that beta-blockers may mask tachycardia occurring with hypoglycemia. Patients treated with a beta-adrenergic receptor blocking agent plus a catecholamine depletor should be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension. When discontinuing therapy in patients receiving beta-blockers and clonidine concurrently, the beta-blocker should be discontinued slowly over several days before the gradual withdrawal of clonidine. Literature reports suggest that oral calcium antagonists may be used in combination with beta-adrenergic blocking agents when heart function is normal, but should be avoided in patients with impaired cardiac function. Hypotension, AV conduction disturbances, and left ventricular failure have been reported in some patients receiving beta-adrenergic blocking agents when an oral calcium antagonist was added to the treatment regimen. Hypotension was more likely to occur if the calcium antagonist were a dihydropyridine derivative, eg, nifedipine, while left ventricular failure and AV conduction disturbances, including complete heart block, were more likely to occur with either verapamil or diltiazem. Pregnancy Category C. In a study in which pregnant rats received betaxolol, the highest dose (600 X MRHD) was associated with increased postimplantation loss, reduced litter size and weight, and an increased incidence of skeletal and visceral abnormalities, which may have been a consequence of drug-related maternal toxicity. Other than a possible increased incidence of incomplete descent of testes and sternebral reductions, betaxolol (6 X MRHD and 60 X MRHD) caused no fetal abnormalities. In a second study with a different strain of rat, betaxolol (300 X MRHD) was associated with maternal toxicity and an increase in resorptions, but no teratogenicity. In a study in which pregnant rabbits received betaxolol (54 X MRHD), a marked increase in postimplantation loss occurred at the highest dose. In a peri- and postnatal study in rats, betaxolol (380 X MRHD) was associated with a marked increase in total litter loss within 4 days postpartum. In surviving offspring, growth and development were also affected. There are no adequate and well-controlled studies in pregnant women. Kerlone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Since Kerlone is excreted in human milk caution should be exercised when Kerlone is administered to a nursing mother. Safety and efficacy in children have not been established. Kerlone may produce bradycardia more frequently in elderly patients.

Adverse Reactions: Kerlone has been associated with the development of antinuclear antibodies (5.3%). Betaxolol adverse events reported in U.S. controlled studies: bradycardia (8.1), symptomatic bradycardia (0.8), edema (1.8), headache (6.5), dizziness (4.5), fatigue (2.9), lethargy (2.8), insomnia (1.2), nervousness (0.8), bizarre dreams (1.0), depression (0.8), impotence (1.2), dyspnea (2.4), pharyngitis (2.0), rhinitis (1.4), upper respiratory infection (2.6), dyspepsia (4.7), nausea (1.6), diarrhea (2.0), chest pain (2.4), arthralgia (3.1), rash (1.2). Betaxolol adverse events reported in European controlled clinical trials: bradycardia (5.8), symptomatic bradycardia (1.9), palpitation (1.9), edema (1.3), cold extremities (1.9), headache (14.8), dizziness (14.8), fatigue (9.7), asthenia (7.1), insomnia (5.0), paresthesia (1.9), nausea (5.8), dyspepsia (3.9), diarrhea (1.9), chest pain (7.1), joint pain (5.2), myalgia (3.2). The following adverse events reported in less than 2% of patients occurred under conditions where a causal relationship is uncertain: flushing, salivation, sweating, allergy, fever, malaise, pain, rigors, angina pectoris, arrhythmia, heart failure, hypertension, hypotension, myocardial infarction, thrombosis, syncope, neuropathy, numbness, speech disorder, stupor, tremor, twitching, anorexia, constipation, dry mouth, increased appetite, mouth ulceration, rectal disorders, vomiting, dysphagia, earache, labyrinth disorders, tinnitus, deafness, leucocytosis, lymphadenopathy, thrombocytopenia, increased AST, increased ALT, acidosis, diabetes, hypercholesterolemia, hyperglycemia, hyperkalemia, hyperlipemia, hyperuricemia, hypokalemia, weight gain, increased LDH, arthropathy, neck pain, muscle cramps, tendonitis, abnormal thinking, amnesia, confusion, emotional lability, hallucinations, decreased libido, breast pain, breast fibroadenosis, menstrual disorder, prostatitis, bronchitis, bronchospasm, cough, epistaxis, flu, pneumonia, sinusitis, pruritus, skin disorders, abnormal taste, taste loss, cystitis, dysuria, proteinuria, abnormal renal function, renal pain, cerebrovascular disorder, leg cramps, peripheral ischemia, thrombophlebitis, abnormal lacrimation, abnormal vision, conjunctivitis, dry eyes, iritis, cataract. Although not reported in clinical studies with betaxolol, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and may be considered potential adverse effects of betaxolol: reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability with slightly clouded sensorium, and decreased performance on neuropsychometric tests, intensification of AV block and congestive heart failure (or cardiac failure), erythematous rash, fever combined with aching and sore throat, laryngospasm, respiratory distress, agranulocytosis, thrombocytopenic purpura, and nonthrombocytopenic purpura, mesenteric arterial thrombosis, ischemic colitis, reversible alopecia, Peyronie's disease, Raynaud's phenomena, skin rashes and/or dry eyes, and oculomucocutaneous syndrome.

10/27/89 • P90-L317V

Address medical inquiries to:
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Medical & Scientific Information Department
4901 Searle Parkway
Skokie, IL 60077

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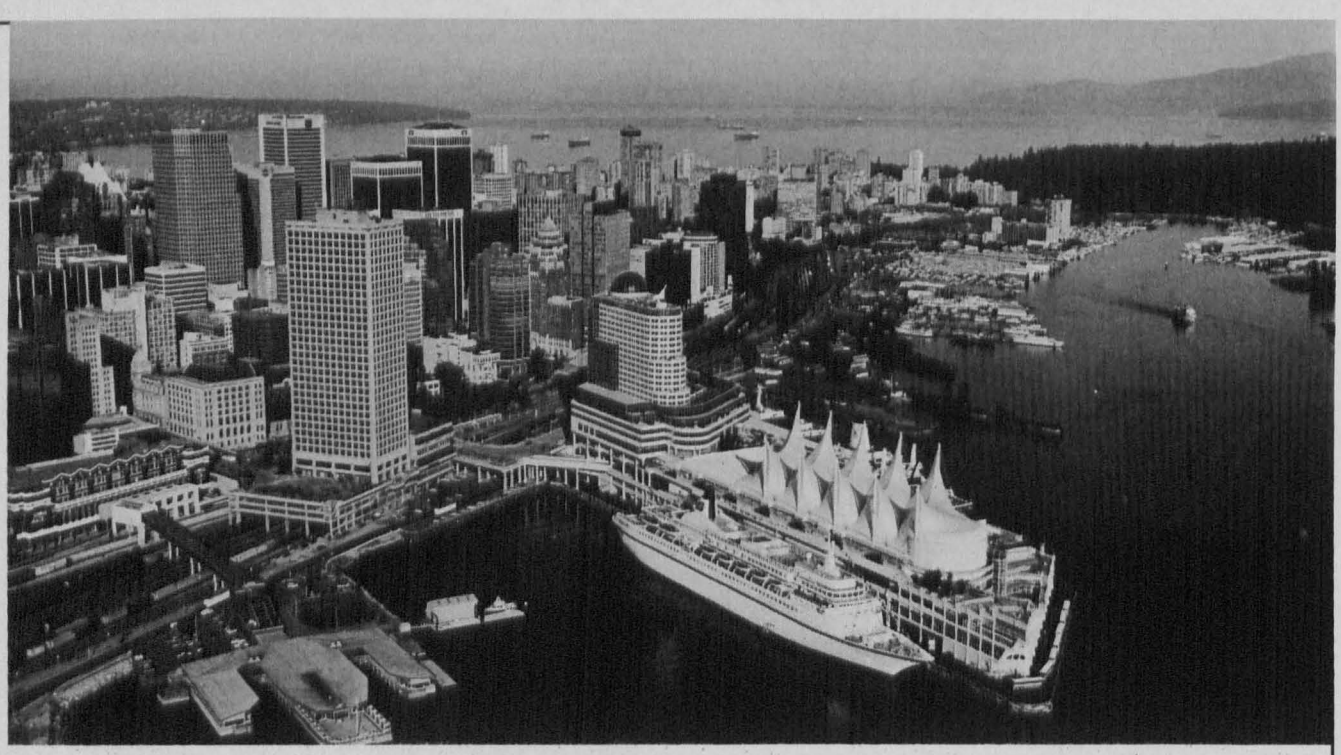

THE WORLD ORGANIZATION OF FAMILY DOCTORS

13TH WONCA WORLD CONFERENCE ON FAMILY MEDICINE

FAMILY MEDICINE IN THE 21ST CENTURY

MAY 9 TO 14, 1992

VANCOUVER BRITISH COLUMBIA CANADA

Hosted by THE COLLEGE OF FAMILY PHYSICIANS OF CANADA AND THE BRITISH COLUMBIA CHAPTER

Keynote speakers will focus on the 1992 status of world health, the consequences in ten years if current trends continue, strategies that could change our behaviour in appropriate ways, and how we might contribute to the political will needed to meet the anticipated challenges.

Complementing the daily sessions will be a large commerical and scientific exhibit area open daily for delegates.

Family physicians, academies, colleges, university departments and research units are invited to submit specific proposals for presentations. Free-standing papers, poster sessions, symposia and workshops are all channels through which you or your organization can participate.

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Vancouver, Canada's third largest city, is the jewel of North America's Pacific Coast. Set in the magnificent natural harbour surrounded by snow-capped mountains, lush forests and picturesque bays and coves, Vancouver is not only one of the most beautiful cities in the world, but also clean, orderly and safe. Vancouver is rich in the colour and life of ethnic variety and offers visitors an almost limitless choice of activities.

Blocks of bedrooms have been reserved for conference delegates in a wide variety of downtown hotels.

CLIMATE
May is early summer with temperatures ranging from 15 degrees C to 20 degrees C (60 degrees F to 70 degrees F). Evening temperatures are rarely below 10 degrees C (50 degrees F).

LANGUAGE
The official languages of the World Conference are English and French.

THE VANCOUVER TRADE AND CONVENTION CENTRE
A spectacular venue for the conference. The Centre is located in the heart of the city, on the ocean, overlooking the coastal mountains. The state-of-the-art facility has spacious well-equipped meeting rooms and is convenient to hotels, shops and restaurants.

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The most prescribed calcium channel blocker for hypertension[1] gets even better

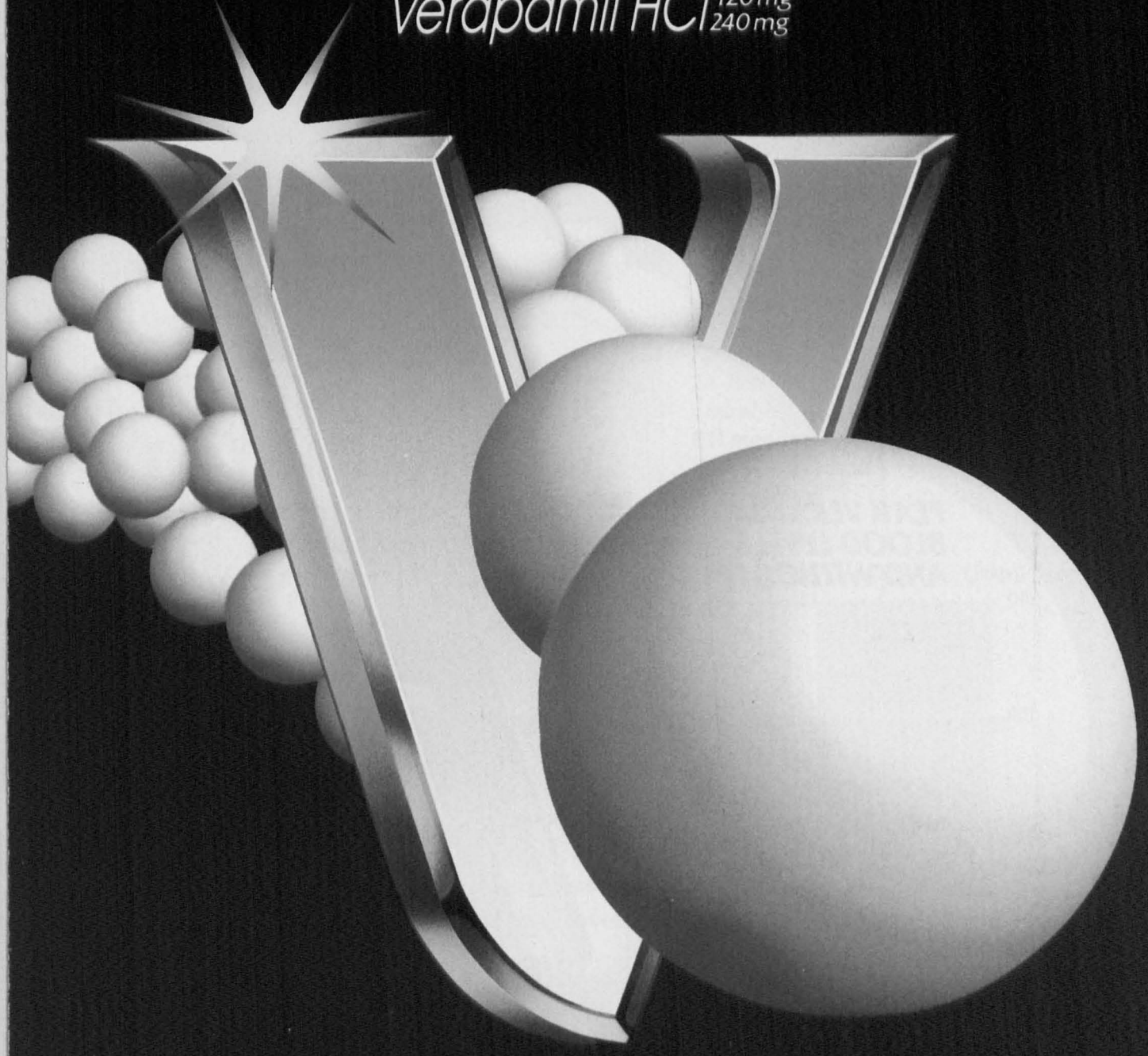
INTRODUCING

New ***ONCE-A-DAY***

VERELAN®

PELLET-FILLED CAPSULES

Verapamil HCl 120 mg 240 mg



Please see brief summary of Prescribing Information on last page.

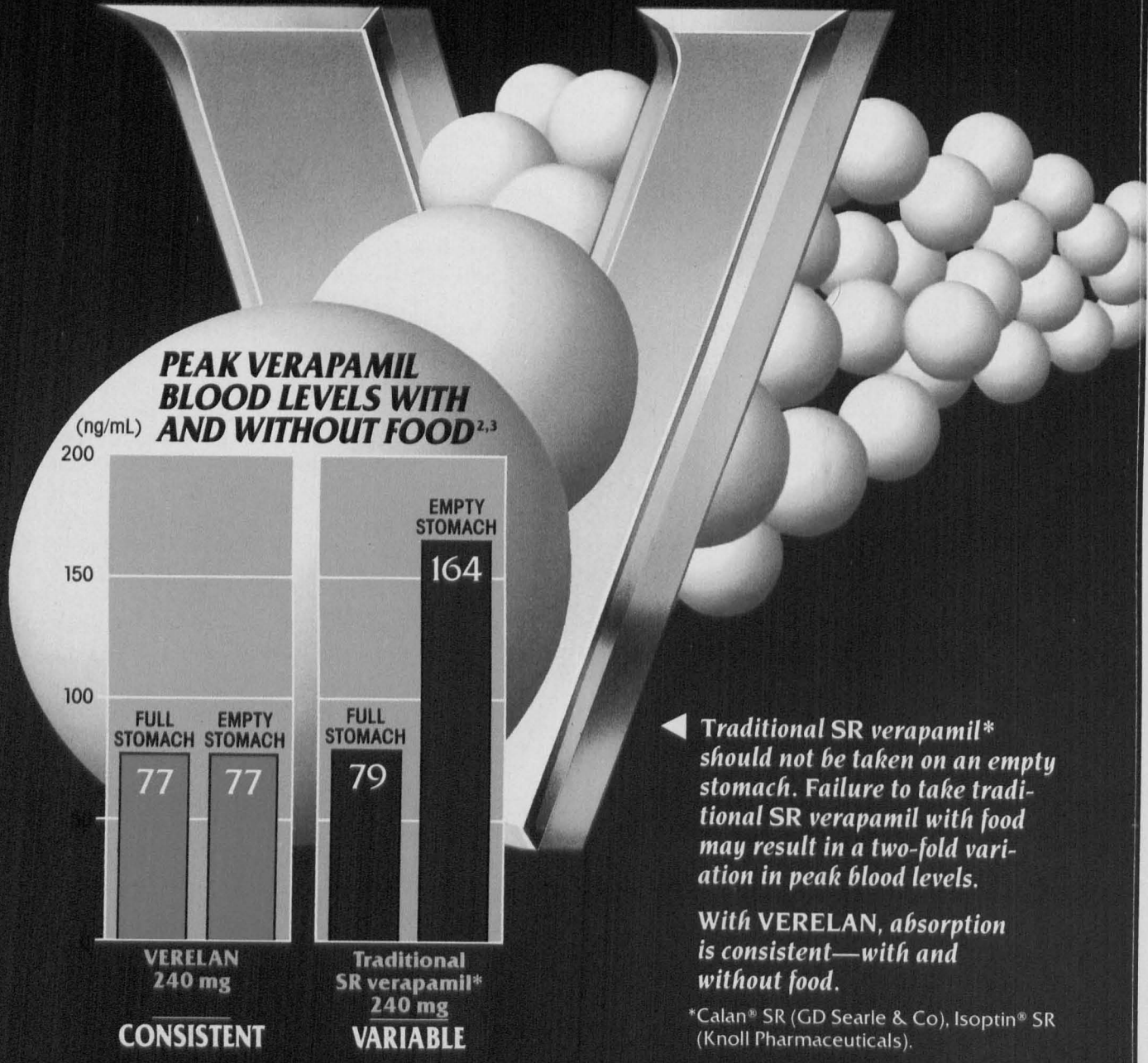
New

ONCE-A-DAY VERELAN®

PELLET-FILLED CAPSULES

Verapamil HCl 120 mg 240 mg

Verapamil without the food variable



◀ ***Traditional SR verapamil* should not be taken on an empty stomach. Failure to take traditional SR verapamil with food may result in a two-fold variation in peak blood levels.***

With VERELAN, absorption is consistent—with and without food.

*Calan® SR (GD Searle & Co), Isoptin® SR (Knoll Pharmaceuticals).

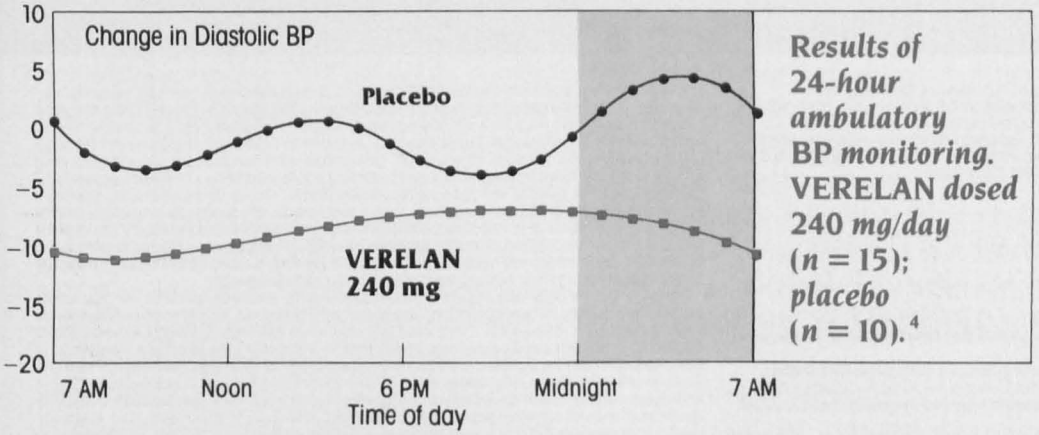
ENGINEERED WITH A NEW PATENTED DELIVERY TECHNOLOGY FOR HYPERTENSION*

Eliminates the food requirement of traditional SR verapamil† therapy[2]—more assurance of proper dosing

- With VERELAN, food intake is not required for consistent absorption. Traditional SR verapamil must be taken with food to achieve the desired absorption profile[2]

Engineered to provide reliable 24-hour blood pressure control

- Maintains control throughout the early morning hours, the period usually associated with greatest cardiovascular risk



***Results of 24-hour ambulatory BP monitoring.* VERELAN *dosed 240 mg/day* ($n = 15$); *placebo* ($n = 10$).[4]**

- Maintains 24-hour effectiveness in reducing elevated blood pressure—with one daily dose.

Enhances convenience

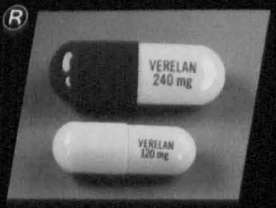
- Patients may not be able to take traditional SR verapamil on a full stomach as recommended
- VERELAN can be taken with or without food—thus eliminating the variation in peak levels observed with traditional SR verapamil therapy if taken on an empty stomach[2,3]
- VERELAN can be taken once a day at all doses, even for patients requiring doses over 240 mg per day
- Constipation, which can be easily managed in most patients, is the most frequently reported side effect of verapamil

*US Patent Number: 4,863,742
†Calan® SR (GD Searle & Co), Isoptin® SR (Knoll Pharmaceuticals).

Please see brief summary of Prescribing Information on next page.

New

ONCE-A-DAY VERELAN®



PELLET-FILLED CAPSULES

Verapamil HCl 120 mg 240 mg

Verapamil without the food variable

- New absorption profile
- Advanced convenience
- Advanced dosing simplicity

The usual dose is 240 mg once daily. If adequate response is not obtained, the dose may be titrated up to 360 mg or 480 mg once daily. VERELAN 120 mg is available for patients requiring lower dose verapamil therapy.

References: 1. Pharmaceutical Data Services, Alpha Data Services, December, 1989.
2. *Physicians' Desk Reference (PDR®).* 44th ed. Oradell, NJ: Medical Economics Co Inc; 1990: 1117-1119 (Isoptin SR):2053-2056 (Calan SR). 3. Data on file, Lederle Laboratories, Pearl River, NY.
4. Bottini PB, Carr AA, Rhoades RE, Prisant LM, O'Brien DE. Dose response of a new once daily verapamil capsule confirmed by ambulatory blood pressure monitoring. Presented at the Fifth Scientific Meeting of the American Society of Hypertension; May 17-21, 1990; New York, NY. Abstract.

Brief Summary
VERELAN® Verapamil HCl
Sustained-Release Pellet-Filled Capsules

For complete Prescribing Information, consult package insert.

CLINICAL PHARMACOLOGY: Food does not affect the extent or rate of the controlled absorption of verapamil from the VERELAN capsule.

Atrioventricular block can occur in patients without preexisting condition defects (see **WARNINGS**).

Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **WARNINGS**).

In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see **PRECAUTIONS**), the volume of distribution is increased, and plasma clearance reduced to about 30% of normal.

CONTRAINDICATIONS: Severe LV dysfunction (see **WARNINGS**), hypotension (systolic pressure <90 mmHg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), second- or third-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), (see **WARNINGS**), hypersensitivity to verapamil.

WARNINGS: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction <30%) or moderate-to-severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. Control milder heart failure with optimum digitalization and/or diuretics before VERELAN is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported.

Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (second- and third-degree, 0.8%). Development of marked first-degree block or progression to second- or third-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, second-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

PRECAUTIONS: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. Interaction between cimetidine and chronically administered verapamil has not been studied. In healthy volunteers, clearance of verapamil was reduced or unchanged. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully.

Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. **Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. Safety and efficacy of verapamil in children below the age of 18 years have not been established.

ADVERSE REACTIONS: In clinical trials with 285 hypertensive patients on VERELAN *verapamil HCL sustained-release pellet-filled capsules* for more than 1 week, the following adverse reactions were reported: constipation (7.4%); headache (5.3%); dizziness (4.2%); lethargy (3.2%); dyspepsia (2.5%); rash (1.4%); ankle edema (1.4%); sleep disturbance (1.4%); myalgia (1.1%). In clinical trials of other formulations of verapamil HCl (N=4,954), the following reactions have occurred at rates greater than 1.0%: constipation (7.3%); dizziness (3.3%); nausea (2.7%); hypotension (2.5%); edema (1.9%); headache (2.2%); rash (1.2%); CHF/pulmonary edema (1.8%); fatigue (1.7%); bradycardia (HR<50/min) (1.4%); AV block-total 1°, 2°, 3° (1.2%); 2° and 3° (0.8%); flushing (0.6%); elevated liver enzymes (see WARNINGS).

The following reactions, reported in 1.0% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain.

Cardiovascular: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope. **Digestive System:** diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia. **Hemic and Lymphatic:** ecchymosis or bruising. **Nervous System:** cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence. **Respiratory:** dyspnea. **Skin:** arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme. **Special Senses:** blurred vision. **Urogenital:** gynecomastia, impotence, increased urination, spotty menstruation.

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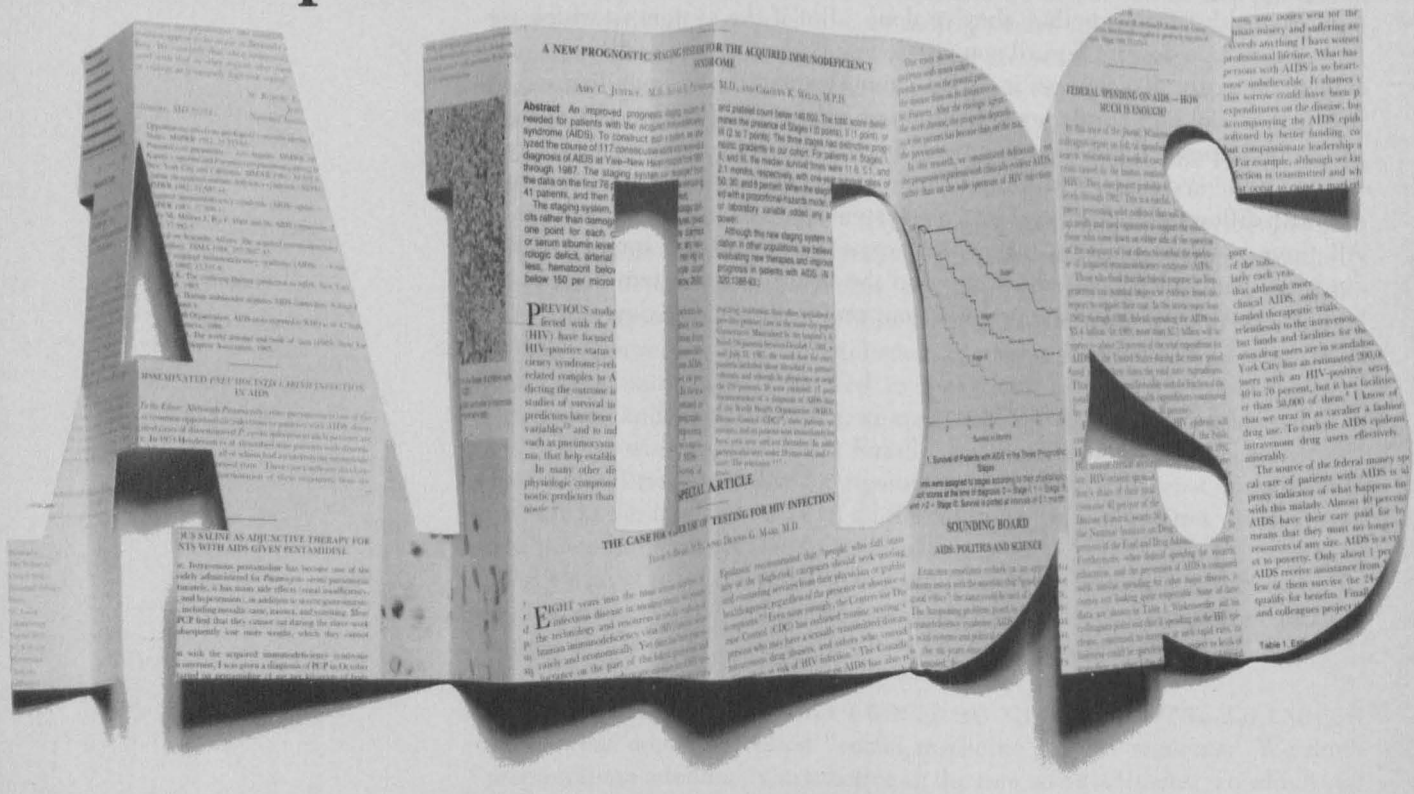

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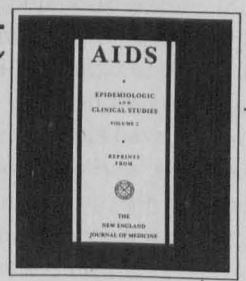

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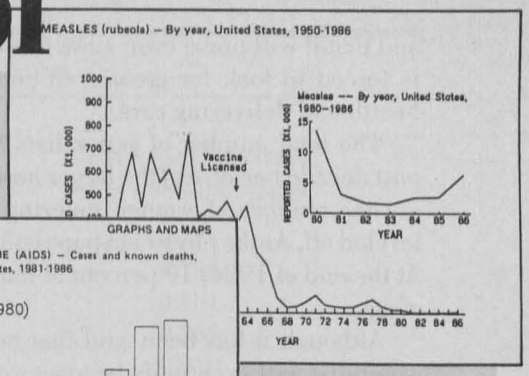

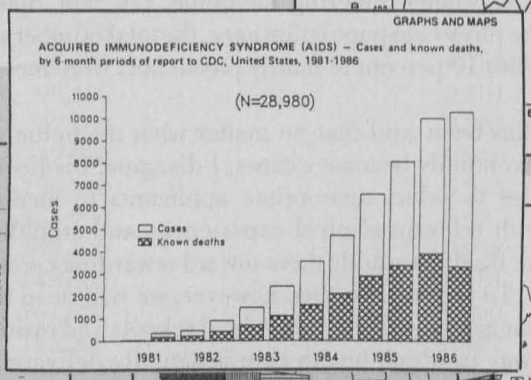

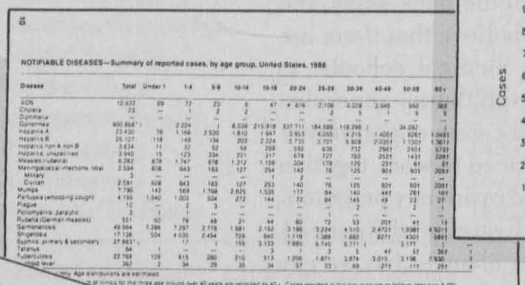

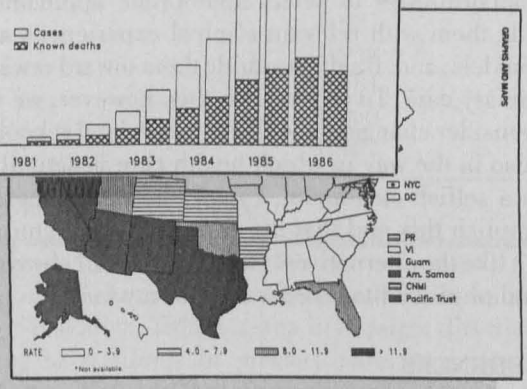

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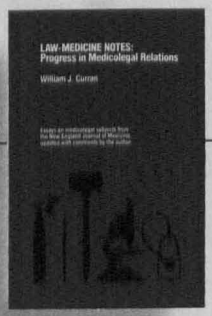

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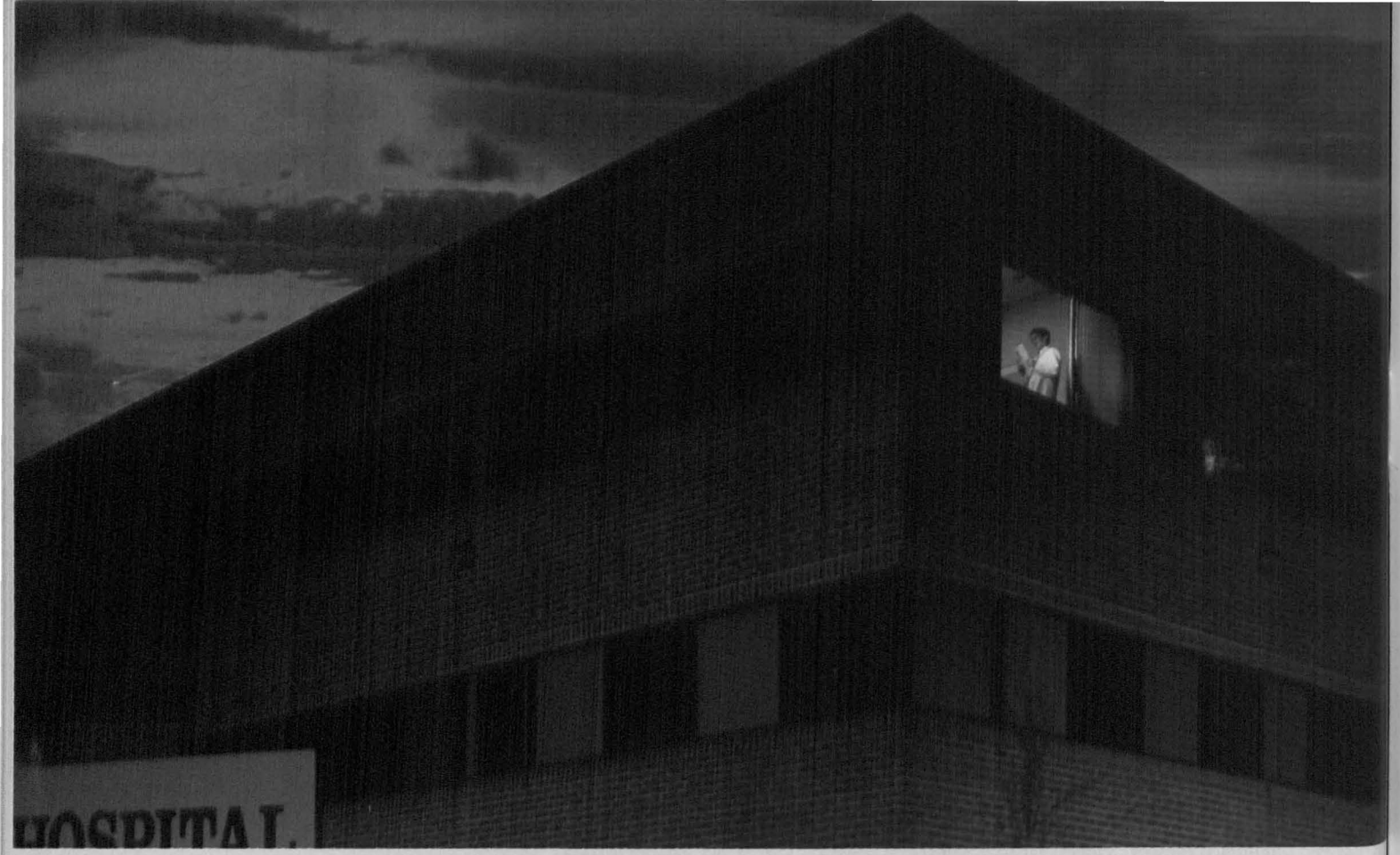

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INDICATIONS AND USAGE: TENORETIC is indicated in the treatment of hypertension. This fixed dose combination drug is not indicated for initial therapy of hypertension. If the fixed dose combination represents the dose appropriate to the individual patient's needs, it may be more convenient than the separate components.

CONTRAINDICATIONS: TENORETIC is contraindicated in patients with: sinus bradycardia; heart block greater than first degree; cardiogenic shock; overt cardiac failure (see WARNINGS); anuria; hypersensitivity to this product or to sulfonamide-derived drugs.

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, TENORETIC should be administered cautiously. Both digitalis and atenolol slow AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients receiving TENORETIC should be digitalized and/or be given additional diuretic therapy. Observe the patient closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, TENORETIC therapy should be withdrawn.

Renal and Hepatic Disease and Electrolyte Disturbances: Since atenolol is excreted via the kidneys, TENORETIC should be used with caution in patients with impaired renal function.

In patients with renal disease, thiazides may precipitate azotemia. Since cumulative effects may develop in the presence of impaired renal function, if progressive renal impairment becomes evident, TENORETIC should be discontinued.

In patients with impaired hepatic function or progressive liver disease, minor alterations in fluid and electrolyte balance may precipitate hepatic coma. TENORETIC should be used with caution in these patients.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORETIC is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORETIC should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta,-selectivity, however, TENORETIC may be used with caution in patients with bronchospastic disease who do not respond to or cannot tolerate, other antihypertensive treatment. Since beta,-selectivity is not absolute, the lowest possible dose of TENORETIC should be used and a beta,-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: It is not advisable to withdraw beta-adrenoreceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as ether, cyclopropane, and trichloroethylene. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

Beta blockers are competitive inhibitors of beta-receptor agonists and their effects on the heart can be reversed by administration of such agents; eg, dobutamine or isoproterenol with caution (see section on Overdosage).

Metabolic and Endocrine Effects: TENORETIC may be used with caution in diabetic patients. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses atenolol does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Insulin requirements in diabetic patients may be increased, decreased or unchanged; latent diabetes mellitus may become manifest during chlorthalidone administration.

Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORETIC therapy is to be withdrawn should be monitored closely.

Because calcium excretion is decreased by thiazides, TENORETIC should be discontinued before carrying out tests for parathyroid function. Pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy; however, the common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen.

Hyperuricemia may occur, or acute gout may be precipitated in certain patients receiving thiazide therapy.

PRECAUTIONS: Electrolyte and Fluid Balance Status: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Patients should be observed for clinical signs of fluid or electrolyte imbalance; ie, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Measurement of potassium levels is appropriate especially in elderly patients, those receiving digitalis preparations for cardiac failure, patients whose dietary intake of potassium is abnormally low, or those suffering from gastrointestinal complaints.

Hypokalemia may develop especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (eg, increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements or foods with a high potassium content.

Any chloride deficit during thiazide therapy is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Drug Interactions: TENORETIC may potentiate the action of other antihypertensive agents used concomitantly. Patients treated with TENORETIC plus a catecholamine depletor (eg, reserpine) should be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope or postural hypotension.

Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude the therapeutic effectiveness of norepinephrine. Thiazides may increase the responsiveness to tubocurarine.

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such preparations with TENORETIC.

Should it be decided to discontinue therapy in patients receiving TENORETIC and clonidine concurrently, the TENORETIC should be discontinued several days before the gradual withdrawal of clonidine.

Other Precautions: In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. The possible exacerbation or activation of systemic lupus erythematosus has been reported. The antihypertensive effects of thiazides may be enhanced in the postsympathectomy patient.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose,* did not indicate a carcinogenic potential of atenolol. A third (24 month) rat study, employing doses of 500 and 1,500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose*) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), in vivo cytogenetics test (Chinese hamster) or Ames test (*S typhimurium*).

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose*) was unaffected by atenolol administration.

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Animal Toxicology: Six month oral studies were conducted in rats and dogs using TENORETIC doses up to 12.5 mg/kg/day (atenolol/chlorthalidone 10/2.5 mg/kg/day — approximately five times the maximum recommended human antihypertensive dose*). There were no functional or morphological abnormalities resulting from dosing either compound alone or together other than minor changes in heart rate, blood pressure and urine chemistry which were attributed to the known pharmacologic properties of atenolol and/or chlorthalidone.

Chronic studies of atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human antihypertensive dose*, respectively).

Use in Pregnancy: **Pregnancy Category C**. TENORETIC was studied for teratogenic potential in the rat and rabbit. Doses of atenolol/chlorthalidone of 8/2, 80/20, and 240/60 mg/kg/day were administered orally to pregnant rats with no teratologic effects observed. Two studies were conducted. In the first study, pregnant rabbits were dosed with 8/2, 80/20, and 160/40 mg/kg/day of atenolol/chlorthalidone. No teratologic changes were noted, embryonic resorptions were observed at all dose levels (ranging from approximately 5 times to 100 times the maximum recommended human dose*). In a second rabbit study, doses of atenolol/chlorthalidone were 4/1, 8/2, and 20/5 mg/kg/day. No teratogenic or embryotoxic effects were demonstrated. It is concluded that the no-effect level for embryonic resorptions is 20/5 mg/kg/day of atenolol/chlorthalidone (approximately ten times the maximum recommended human dose*). TENORETIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Atenolol—Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human antihypertensive dose.* Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human antihypertensive dose.* There are no adequate and well-controlled studies in pregnant women.

*Based on the maximum dose of 100 mg/day in a 50 kg patient weight.

Chlorthalidone—Thiazides cross the placental barrier and appear in cord blood. The use of chlorthalidone and related drugs in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when atenolol is administered to a nursing woman. Clinically significant bradycardia has been reported in breast fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

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

ADVERSE REACTIONS: TENORETIC is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient. The adverse effects observed for TENORETIC are essentially the same as those seen with the individual components.

Atenolol: The frequency estimates in the following table were derived from controlled studies in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both atenolol and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for atenolol and placebo is similar, causal relationship to atenolol is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the US studies (volunteered side effects) and then from both US and foreign studies (volunteered and elicited side effects):

US STUDIES (ATENOLOL, n=164); PLACEBO, n=206) (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%),dreaming (0%-0%)

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%)

RESPIRATORY (see WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS US AND FOREIGN STUDIES (ATENOLOL, n=399; PLACEBO, n=407):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

During postmarketing experience, the following have been reported in temporal relationship to the use of the drug: reversible alopecia, impotence, elevated liver enzymes and/or bilirubin, and thrombocytopenia.

Chlorthalidone: Cardiovascular: orthostatic hypotension; Gastrointestinal: anorexia, gastric irritation, vomiting, cramping, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; CNS: vertigo, paresthesias, xanthopsia; Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; Hypersensitivity: purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis); Miscellaneous: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness. Clinical trials of TENORETIC conducted in the United States (89 patients treated with TENORETIC) revealed no new or unexpected adverse effects.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects not observed in clinical trials with atenolol but reported with other beta-adrenergic blocking agents should be considered potential adverse effects of atenolol. Nervous System: Reversible mental depression progressing to catatonia; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS); Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis; Hematologic: Agranulocytosis, purpura; Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; Miscellaneous: Peyronie's disease.

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, otitis, and sclerosing serositis attributed to the beta-adrenergic receptor blocking agent, practolol. This syndrome has not been reported with TENORETIC or TENORMIN® (atenolol).

Clinical Laboratory Test Findings: Clinically important changes in standard laboratory parameters were rarely associated with the administration of TENORETIC. The changes in laboratory parameters were not progressive and usually were not associated with clinical manifestations. The most common changes were increases in uric acid and decreases in serum potassium.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED (SEE INDICATIONS)

Chlorthalidone is usually given at a dose of 25 mg daily; the usual initial dose of atenolol is 50 mg daily. Therefore, the initial dose should be one TENORETIC 50 tablet given once a day. If an optimal response is not achieved, the dosage should be increased to one TENORETIC 100 tablet given once a day.

When necessary, another antihypertensive agent may be added gradually beginning with 50 percent of the usual recommended starting dose to avoid an excessive fall in blood pressure.

Since atenolol is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of atenolol occurs until creatinine clearance falls below 35 mL/min/1.73m² (normal range is 100-150 mL/min/1.73m²); therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (mL/min/1.73m²)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

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