For first-line therapy in mild-to-moderate hypertension
Discover the classic benefits of a beta-blocker and a diuretic...now at low doses for a side-effect profile comparable to placebo

ZIAC controls mild-to-moderate hypertension in up to 80% of patients
ZIAC controls blood pressure for a full 24 hours for true once-a-day dosing
ZIAC minimizes traditional beta-blocker- and HCTZ-associated metabolic effects (hypokalemia, hyperuricemia, hypercholesterolemia, hyperglycemia)

*The two most common side effects — dizziness and fatigue — occurred at rates comparable to placebo.
*Clinical trial response rates were: 2.5 mg—61%; 5 mg—73%; 10 mg—80%.
ZIAC is contraindicated in patients in cardiogenic shock, overt cardiac failure (see WARNINGS section of full Prescribing Information), second- or third-degree AV block, marked sinus bradycardia, anuria, and hypersensitivity to either component of this product or to other sulfonamide-derived drugs.
Please see Brief Summary of Prescribing Information on adjacent page.
ZIAC® (Bisoprolol Fumarate and Hydrochlorothiazide) Tablets

ZIAC® tablets contain bisoprolol fumarate 6.25 mg and hydrochlorothiazide 12.5 mg. 

**CLINICAL PHARMACOLOGY**

**Renal:***

Hydrochlorothiazide, a thiazide diuretic, increases the urine excretion of sodium and chloride, which is accompanied by a decrease in plasma volume, decrease in blood pressure, and a reduction in renin levels. This reduces renin release, which in turn decreases aldosterone release and causes a diuresis and natriuresis. 

**Musculoskeletal:***

Hydrochlorothiazide exerts a diuretic effect and decreases plasma volume which may place a strain on already compromised myocardium and may increase myocardial oxygen requirements. 

**Interactions:***

The effects of hydrochlorothiazide may be potentiated by concurrent use of angiotensin-converting enzyme inhibitors such as captopril and other diuretics that produce potassium loss, and by amphotericin B, furosemide, and pentamidine. 

**WARNINGS:***

**Beta-Blockers:**

ZIAC is contraindicated in patients who exhibit bronchospastic pulmonary disease, such as asthma or chronic bronchitis.

**Drug-Interactions:**

Mechanism of Action:

ZIAC combines a 

- **Bisoprolol Fumarate:** 6.25 mg, which is a selective beta-blocker that blocks beta-adrenergic receptors. The duration of its action is about 24 hours, but it is not expected to be excreted renally.

- **Hydrochlorothiazide:** 12.5 mg, which is a thiazide diuretic that decreases plasma volume and reduces peripheral vascular resistance by blocking the production of aldosterone. It is excreted renally.

**ADVERSE REACTIONS** (Premarketing Experience)

**Cardiac:**

- Bradycardia
- Hypotension
- Angina
- Arrhythmias

**Respiratory:**

- Cough
- Bronchitis

**Gastrointestinal:**

- Diarrhea
- Nausea
- Abdominal cramps

**Special Senses:**

- Blurred vision

**Other:**

- Fatigue

**Patients With Bronchospastic Pulmonary Disease:**

Patients with bronchospastic pulmonary disease should not receive beta-blockers. Abrupt withdrawal of hydrochlorothiazide may precipitate bronchospasm.

**Drug-Interactions:**

1. Bisoprolol fumarate:

- **Effects on Other Drugs:**

  - **Hydrochlorothiazide:**

    - Decreased levels of potassium, magnesium, and sodium.
    - Increased levels of creatinine and uric acid.

- **Effects on Other Agents:**

  - **Beta-Blockers:**

    - Increased levels of serum uric acid.
    - Decreased levels of potassium, magnesium, and sodium.

- **Other Agents:**

  - **ACE Inhibitors:**

    - Increased levels of serum potassium.

**PRECAUTIONS**

**Hypotension:**

ZIAC should be used with caution in patients with impaired renal function or those on dialysis. 

**Hypokalemia:**

ZIAC should be used with caution in patients with impaired renal function or on dialysis. 

**Trapped Air:**

ZIAC should be used with caution in patients with impaired renal function or on dialysis. 

**Hyperkalemia:**

ZIAC should be used with caution in patients with impaired renal function or on dialysis. 

**Hypernatremia:**

ZIAC should be used with caution in patients with impaired renal function or on dialysis. 

**Hypoglycemia:**

ZIAC should be used with caution in patients with impaired renal function or on dialysis. 

**Drug-Interactions:**

ZIAC should be used with caution in patients with impaired renal function or on dialysis.

**REPEATED Dosing:**

ZIAC should be used with caution in patients with impaired renal function or on dialysis.

**SPONTANEOUSLY REPORTED ADVERSE REACTIONS:**

The following adverse reactions have been reported with bisoprolol fumarate and/or hydrochlorothiazide: 

- **Cardiac:** Bradycardia, heart block, hypotension, angina, arrhythmias, and heart failure.
- **Respiratory:** Cough, bronchitis, and dyspnea.
- **Gastrointestinal:** Diarrhea, nausea, abdominal cramps, and decreased appetite.
- **Special Senses:** Blurred vision.
- **Other:** Fatigue.

**ADVERSE EXPERIENCES WITH ZIAC® (Bisoprolol Fumarate and Hydrochlorothiazide) Tablets**

- **Cardiac:** Bradycardia, heart block, hypotension, angina, arrhythmias, and heart failure.
- **Respiratory:** Cough, bronchitis, and dyspnea.
- **Gastrointestinal:** Diarrhea, nausea, abdominal cramps, and decreased appetite.
- **Special Senses:** Blurred vision.
- **Other:** Fatigue.

**REFERENCES:**


75% of primary care physicians have treated patients with HIV infection.
Do you have the information you need?

Every month, AIDS Clinical Care brings you the latest clinically relevant information in a concise, easy-to-read newsletter.

**Feature articles** written by leading AIDS clinicians provide hands-on information about the management of HIV-related diseases. Topics include:

- AIDS/HIV Clinical Trial Updates
- Antiretroviral Therapy Controversies
- Treating and Preventing Opportunistic Infections
- HIV Infection in Women
- NIH Recommendations
- Pediatric AIDS
- Drug Interactions
- Psychosocial Issues
- Nutrition in HIV

The new **Case History** column answers clinical questions on the complex, overlapping manifestations of HIV infection by presenting actual case histories with diagnoses and patient follow-up.

**Research Notes** summarize and comment on the most relevant articles from the medical literature. **Charts and tables** clearly show clinical presentations, diagnostic methods, treatment regimens, and epidemiologic trends.

**EDITOR**

Deborah J. Cotton, MD, MPH
Infectious Disease Unit, Massachusetts General Hospital; Assistant Professor of Medicine, Harvard Medical School; Assistant Professor of Health Policy and Management, Harvard School of Public Health, Boston.

Subscribe today. Simply fill out the coupon, or order by FAX: (617) 893-0413

☐ YES, please start my subscription to AIDS Clinical Care.
I will receive 12 monthly issues delivered first class for the special price of $89.
☐ Payment enclosed*  ☐ Bill me  ☐ Charge my credit card  ☐ VISA  ☐ MasterCard  ☐ AmEx
Card #_________ Exp Date_________
Signature__________________________________________
Name_________________________ (Please print)
Address______________________________________________
City_________________________ State_________ Zip_________
Specialty__________________________
In 1987, Galveston Manufacturing introduced the Galveston Metacarpal Brace™. After over seven years of clinical use, the brace has proven successful in treating metacarpal shaft fractures. Galveston Manufacturing has continued serving the medical community, bringing you the latest quality fracture management products at affordable prices. So far this year we've introduced three new products to our line; the THUMZ'UP® functional thumb splint, the ORFIZIP® casting system and the PLAST-O-FIT® thermoplastic bandage system.

For ordering information or a product catalog, simply call 1-800-634-3309.
NOW you can HEAR what you've been missing!

**Announcing Journal Watch - The Audio Cassette Service** — the fastest way to keep up with what's new and important in medicine.

Twice a month, Journal Watch — The Audio Cassette Service brings you 60 minutes of clear, concise summaries of the latest advances published in more than 20 major journals.

**Journal Watch** — The Audio Cassette Service is written exclusively by practicing physicians. With your subscription you can earn two Category I CME credits per one hour program — at no additional cost.

Using Journal Watch's convenient, easy to listen to audio cassettes, you can schedule when and where to listen.

- In your car
- At the gym
- During meal time
- Between patients
- During your daily routines
- Or simply spare moments of the day

Brought to you by two leaders in medical information — Audio-Digest Foundation, producers of "The Thirteen Spoken Medical Journals®" and the Massachusetts Medical Society, publishers of the New England Journal of Medicine, Journal Watch (the newsletter), and AIDS Clinical Care.

**FREE SAMPLE CASSETTE!**

☐ YES! Please rush my FREE sample cassette, Volume 1, Issue 1 of Journal Watch — The Audio Cassette Service. If I decide to become a charter subscriber, I'll receive 9 months, 18 issues at the special introductory price of $113.75.

MAIL TO:
Audio-Digest Foundation®
A Non-Profit Subsidiary of the California Medical Association
1577 East Chevy Chase Drive
Glendale, CA 91206

Or Call Toll Free: 1-800-423-2308
(8 am to 5 pm, Pacific Time)

FAX Toll Free: 1-800-845-4375
(24 hours)
For all your arthritis patients—

**HAND IT TO ZOSTRIX®**
topical analgesic cream

When an NSAID is needed but localized pain persists...

**FIRST...**
For safe relief for all your arthritis patients

ZOSTRIX does not interfere with systemic medications. No GI, hepatic, or renal effects have been reported.

1. Rub a small dab on the painful joint 3 or 4 times daily without fail. Relief should start in a few days, with maximum relief within 2 weeks.


© 1994 GenDerm Corporation
ATTENTION
DIPLOMATES OF THE ABFP
ADDRESS CHANGE FORM

The Board prefers the use of professional addresses, because the address given will become your "address of record" with the Board and will be published in our Directory of Diplomates.

Current addresses for all Diplomates are necessary for communication from the Board relating to the Examinations, up-dated Recertification information, etc., as well as to ensure the receipt of The Journal of the American Board of Family Practice.

Name ____________________________________________________

Current Address
Street ______________________________
______________________________
City/State ____________________________
Zip Code ____________________________

New Address
Street ______________________________
______________________________
City/State ____________________________
Zip Code ____________________________

Effective Date of Change ________________________________

Signature of Diplomate _______________________________

ABFP Identification Number ____________________________
(5-digit number above name on mailing label)

Year of Certification or Recertification __________________

Return to: Ann Stockham
The American Board of Family Practice
2228 Young Drive
Lexington, KY 40505
INFORMATION FOR READERS

The Journal of the American Board of Family Practice
Official Publication of the American Board of Family Practice
2228 Young Drive, Lexington, KY 40505

EDITORS
John P. Geyman, M.D., Editor
Paul R. Young, M.D., Executive Editor
Alfred O. Berg, M.D., Associate Editor
Paul Brucker, M.D., Associate Editor
G. Gayle Stephens, M.D., Associate Editor
Claire Z. Fenwick, Assistant Editor
Ann Stockham, Copy Editor and Assistant Executive Editor
Virginia M. Gessner, Senior Editorial Assistant
Debbie Wilson, Production Assistant Mary K. Lowell, Reference Verification

PUBLISHING SERVICES
Publishing Division, Massachusetts Medical Society
Robert D. Bovenschulte, Vice President for Publishing
William H. Paige, Executive Director for Operations
Christopher R. Lynch, Executive Director for Product Management
Justin R. Spence, Product Manager
Robert Quinn, Reprints

Advertising Sales and Production
Arthur Wilchek, Director
William Healy, Manager, Midwest Accounts
Lewis Wetzel, Manager, Eastern Accounts
Wayne Wickman, Manager, Eastern Accounts
Christine Miller, Manager, Recruitment Advertising
Mary Kaye Howe, Production Manager
Lynne Brochu

Circulation and Product Marketing
Laurie Pass, Director

Electronic Production
Ruth E. Goodman, Director
Tommie Richardson, Coordinator
Sherie Peters, Thomas Gardon, Susan McDonough, Laurie Marcurelle, David Laslaz

Computer Assisted Publishing Support
Leon Barzini, Director
Martha Soole

SUBSCRIPTION INFORMATION AND SERVICES
The Journal of the American Board of Family Practice is supplied free of charge to 50,400 Diplomates and Residents of the American Board of Family Practice. For information please contact:
American Board of Family Practice
2228 Young Drive
Lexington, KY 40505
Tel: (606) 269-5626
FAX: (606) 266-9699

For all other subscribers please contact:
The Journal of the American Board of Family Practice
Subscription Department
1440 Main Street
Waltham, MA 02154-1649
(617) 893-3800, ext. 1199
Telex: 5106017779 NEJM BOS
Fax: (617) 893-0413

SUBSCRIPTION RATES
Domestic International*
Institutions $58.00 $60.00
Physicians $15.00 $45.00
Residents/Students $20.00 $45.00

OTHER SUBSCRIPTION INFORMATION
Diplomates should make address changes on the form accompanying this issue and forward to the Diplomate address listed above. All other subscribers should forward changes to the Waltham, Mass., address listed on this page. Changes must be received at least six weeks in advance of intended move. Please send new address, old address, and expected date of change.

ISSUES NOT RECEIVED
Missing issues will be replaced for up to three months from the issue date without charge. Diplomates and other subscribers who fail to notify the Lexington, Ky., or the Waltham, Mass., office of address changes will not be eligible for free replacement issues. Claims beyond the three-month limit must be prepaid at the backcopy rates. Claims should be sent to either the Diplomate or regular subscriber address listed on this page.

BACK COPIES
If you wish to purchase back copies (issues published prior to your effective start date) of the Journal of the American Board of Family Practice, there is a charge of $12.50 per issue. Contact the Waltham, Mass., address listed above for information.

REPRINTS
Individual copies of articles are available from the Waltham, Mass., office. If you wish to order bulk reprints (minimum order of 100) please contact the Reprint Department (617) 893-3800, ext. 1279, at the Waltham, Mass., office.

COPYRIGHT
Material appearing in the Journal of the American Board of Family Practice is covered by copyright. Copying beyond the quantities permitted under "fair use" as defined by U.S. copyright law is allowed provided the stated fee of $2.00 per page is paid through the Copyright Clearance Center, 21 Congress St., Salem, MA 01970. This consent does not extend to other copying, such as copying for advertising or promotional purposes. Single copies for personal or internal use are allowed at no charge. Nonprofit institutions may make copies provided they obtain prior consent from the Journal of the American Board of Family Practice, Rights and Permissions Department, 1440 Main Street, Waltham, MA 02154-1649, (617) 893-3800, ext. 1413.

INDEXING AND MICROFORM
The Journal of the American Board of Family Practice is indexed in Index Medicus and is available in microform from University Microfilms International.

Information for Readers JABFP
INFORMATION FOR AUTHORS

The Journal of the American Board of Family Practice welcomes for editorial review manuscripts that contribute to family practice as a clinical scientific discipline. High priority is given to reports of clinically relevant studies that have practical implications for improved patient care. Manuscripts are considered in relation to the extent to which they represent original work, their significance to the advancement of family medicine, and their interest to the practicing family physician. Some papers that are accepted by the Journal will be selected for an accompanying guest editorial or concurrent commentary by other invited authors addressing issues raised by the papers. The Journal publishes the following features:

Original Articles. Reports of original research, usually dealing with a clinical, health services, or other clinically relevant study.

Medical Practice. Scholarly articles that relate directly to clinical topics useful in everyday family practice, which may present a diagnostic or therapeutic role of the family physician or reporting studies of what family physicians do in practice.

Clinical Review. In-depth reviews of specific clinical problems, disease entities, or treatment modalities; comprehensive and critical analysis of the literature is required (usual maximum length 5000 words).

Clinical Guidelines and Primary Care. Summaries of major clinical guidelines proposed by various specialty, governmental, or health care organizations, with critical commentary from a primary care perspective.

Family Practice and the Health Care System. Articles reporting studies and scholarly commentary on changing trends and patterns of care in family practice, primary care, and the health care system.

Special Articles. Articles in other areas that may relate to the role of the family physician, education for family practice, or other subjects important to family practice as a clinical specialty.

Brief Reports. Short reports of pilot studies or case reports with a teaching point of clinical relevance (usual length 1000–1500 words).

Family Practice—World Perspective. Papers reporting developments related to the practice or education of family physicians in various countries around the world (usual length 1200–1800 words).

Reflections in Family Practice. Papers in narrative or essay format that illuminate qualitative aspects of family practice, including such areas as ethical issues, the physician–patient relationship, or the diverse roles of the family physician.

Editorial. Focused opinion or commentary that bears on an issue relevant to the field. May or may not accompany an original article in the same issue (usual length 1000–1500 words).

Letters to the Editor. Observations, opinion, or comment on topics under discussion in the Journal, usually not to exceed 500 words.

Book Reviews. Books for review and book reviews should be sent to Dr. John P. Geyman, Editor, the Journal of the American Board of Family Practice, Department of Family Medicine (HQ-30), School of Medicine, University of Washington, Seattle, WA 98195.

The following guidelines are in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals." The current (fourth) edition was published in the February 7, 1991, issue of the New England Journal of Medicine.

MANUSCRIPT SUBMISSION

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 3 copies 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, Department of Family Medicine (HQ-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. If July-August 1994 Vol. 7 No. 4 authors acknowledge by name persons who provided important technical, advisory, or reviewer contributions, the corresponding author should sign the following statement: "I have obtained written permission from all persons named in the acknowledgment."

The Journal expects authors to take public responsibility for their manuscripts, including conception and design of the work, data analysis, writing, and review of the paper. Authors are expected to stand behind the validity of their data and, if asked by the Editor, to submit the actual data for editorial review with the manuscript. In most instances authorship should be limited to 8 authors or fewer, all meeting the above criteria for authorship. Exceptions to these guidelines, especially those involving multisite collaborative research projects, should be discussed on a case-by-case basis with the Editor.

The Journal also expects authors to disclose any commercial associations that might pose a conflict of interest in connection with the submitted article. Consultancies, stock ownership or other equity interests, patent-licensing arrangements, and other kinds of associations that might involve conflict of interest 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.

MANUSCRIPTS

Titles and Authors' Names

With the manuscript, provide a page giving the title of the paper; a running foot of fewer than 40 letter spaces; the name(s) of the author(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. All funding sources supporting the work should be routinely acknowledged on the title page, as should all institutional or corporate affiliations of the authors. Two or four key words should be submitted with the manuscripts to be used for purposes of classification by subject. Use terms from the Medical Subject Headings from Index Medicus when possible.

Abstracts
Use another page to provide an abstract of not more than 200 words. This abstract should be factual, not descriptive, with its content appropriate to the type of paper. For original articles reporting results of studies, a four-paragraph format should be used labeled Background, Methods, Results, and Conclusions. These should briefly describe, respectively, the object of the study, the methods used, the major results, and the author(s) conclusions. Abstracts are not necessary for Brief Reports or World Perspective papers.

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.

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

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 6 or fewer; when there are 7 or more, list the first 6, then "et al." Sample references are as follows:

Standard Journal Article
(List all authors, but if the number exceeds 6, give 6 followed by et al. Note that month and issue number are omitted when a journal has continuous pagination throughout a volume.) Morrow JD, Margolies GR, Rowland J, Roberts LJ 2nd. Evidence that histamine is the causative toxin of scombroid-fish poisoning. N Engl J Med 1991; 324:716-20.

Organization as Author

Book

Chapter in Book

Government Agency

Personal Communications
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 title for each. For footnotes, use the following symbols, in this sequence: *, †, ‡, §, ¶, **, ††, etc. 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. Permissions forms are available from the Editor.

Legends for illustrations should be type-written (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.

Permissions
Every effort (short of changing the patient data) should be made by the authors to protect the anonymity of patients (and relatives) in any published work. If identification is unavoidable, informed consent should be obtained and attached with the submitted letter; in the case of minors or incompetent patients, consent should be obtained from relatives or guardians.

Materials taken from other sources must be accompanied by a written statement from both author and publisher giving permission to the Journal for reproduction. Obtain permission in writing from at least one author of papers still in press, of unpublished data, and of personal communications.

REVIEW AND ACTION
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. Every effort will be made to complete the review process as expeditiously as possible.

Copyright Transfer Forms
Transfer of copyright to the Journal is requested upon acceptance of the material for publication. Copyright transfer is required of all materials to be published in the Journal, including Letters to the Editor and Book Reviews.

Reprints
Authors will receive reprint information and rates when their articles are sent their galley proofs. Reprints ordered at that time will be shipped about 3 weeks after the publication date.

Information for Authors JABFP
The value of treating hypertension in older patients has been clearly established.*
Today, the prevalence of hypertension in people over 60 is greater than 60%.†

Often, PLENDIL represents a good choice for older patients with hypertension.‡

With a simple once-daily dosage regimen, PLENDIL provides a gradual onset of action with continuous 24-hour control. Generally, PLENDIL is well tolerated when administered in recommended doses.¶

Usual dosage range is 5 mg to 10 mg daily. But, patients over 65 may have elevated plasma concentrations of felodipine, and may therefore respond to lower doses of PLENDIL.

PLENDIL: A considerate choice for patients who deserve "special handling."* 

* The ability of calcium channel blockers to reduce morbidity or mortality has not been established.
† Patients over 65, and those with impaired liver function, should have their blood pressure monitored closely during adjustment of PLENDIL and should rarely require doses above 10 mg. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in the Prescribing Information.)
‡ Peripheral edema, generally mild, is the most common adverse experience. PLENDIL is contraindicated in patients who are hypersensitive to this product.

Plendil®
(felodipine) Tablets,
5 mg, 10 mg

Because you consider the whole patient. Please see brief summary of Prescribing Information on page following next page.
synchronous cell hyperplasia compared to control was observed in the esophagogastric groove of nude and female rats in all dose groups. No other drug-related esophagitis or gastric pathology was observed in the rats or with chronic administration in rats and dogs. The latter species, like man, has no anatomical structure comparable to the esophagogastric groove.

Felodipine was not carcinogenic when fed to mice at doses of up to 138.6 mg/kg/day (0.4 mg/kg/day for 0.4-4 mg/kg/day the maximum recommended human dose on a mg/m² basis) for periods of up to 80 weeks in males and 99 weeks in females.

Felodipine did not display any mutagenic activity in vitro in the Ames bacterial mutagenicity test or in the mouse lymphoma forward mutation assay. No carcinogenic potential was seen in the intramuscular test at oral doses up to 2500 mg/kg (505 times the maximum recommended human dose on a mg/m² basis) at a site in vivo in a human hypertensive arm circulation assay.

A fertility study in which male and female rats were administered doses of 3.8, 8.5, and 25.6 mg/kg/day showed no significant effect of felodipine on reproduction performance.

Pregnancy

Category C

Teratogenic Effects: Studies in pregnant rabbits administered doses of 0.04, 0.4, 4.0 mg/kg/day (0.4 mg/kg/day for 0.4-4 mg/kg/day the maximum recommended human dose on a mg/m² basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency of this finding increased as dosages approached threat-related and were noted only at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class and are possibly a result of compensatory blood flow. Similar fetal anomalies were not observed in rats given felodipine.

In a teratology study in chronophorous monkeys no reduction in the size of the terminal phalanges was observed but an abnormal position of the distal phalanges was noted in about 40 percent of the fetuses.

Nongenotoxic Effects: A prolongation of parturition with difficult labor and an increased frequency of fatal and early postnatal deaths were observed in rats at doses higher than 4 mg/kg/day (4 times the maximum human dose on a mg/m² basis) and above.

Significant enlargement of the mammary glands in excess of the normal enlargement for pregnant rabbits was found with doses greater than or equal to 1.2 mg/kg/day (equal to the maximum human dose on a mg/m² basis). This effect occurred only in pregnant rabbits and regressed during lactation. Similar changes in the mammary glands were not observed in rats or monkeys.

There are no adequate and well-controlled studies in pregnant women. If felodipine is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus, possible digital anomalies of the infant, and the potential effects of felodipine on labor and delivery, and on the mammary glands of pregnant females.

Nursing Mothers

It is not known whether this drug is excreted in human milk and because of the potential for serious adverse drug experience to the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In controlled studies in the United States and overseas approximately 3000 patients were treated with felodipine as either the extended-release or the immediate-release formulation.

The most common clinical adverse experiences reported with FLENOIL (Felodipine) administered as monotherapy in all settings and with all dosage forms were: Peripheral Edema, Headache, and Leg Pain.

Adverse experiences that occurred with a frequency of greater than or equal to 2% during monotherapy treatment of patients receiving FLENOIL, without regard to causality are presented in the table below.

Percent of Patients with Adverse Effects in Controlled Trials (Incidence of discontinueable doses shown in parentheses)

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>n = 700</th>
<th>Placebo</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Edema</td>
<td>22.3 (4.2)</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>18 (2.6)</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>6.4 (1.0)</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Leg Pain</td>
<td>5.8 (0.8)</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Gingival Hyperplasia</td>
<td>5.5 (0.1)</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>4.7 (0.1)</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>2.9 (0.1)</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.5 (0.1)</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2.3 (0.1)</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Chest Pain</td>
<td>2.1 (0.1)</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1.9 (0.1)</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Muscle Cramps</td>
<td>1.0 (0.1)</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Palpitation</td>
<td>1.0 (0.1)</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1.8 (0.1)</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>1.6 (0.1)</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.4 (0.1)</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1.6 (0.1)</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Rheumatism</td>
<td>1.6 (0.1)</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Varicose Veins</td>
<td>1.5 (0.1)</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>1.5 (0.1)</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>

In the two dose response studies using FLENOIL, as monotherapy, the following table describes the incidence (percent) of adverse experiences that were dose-related. The incidence of discontinuations due to these adverse experiences are shown in parentheses.