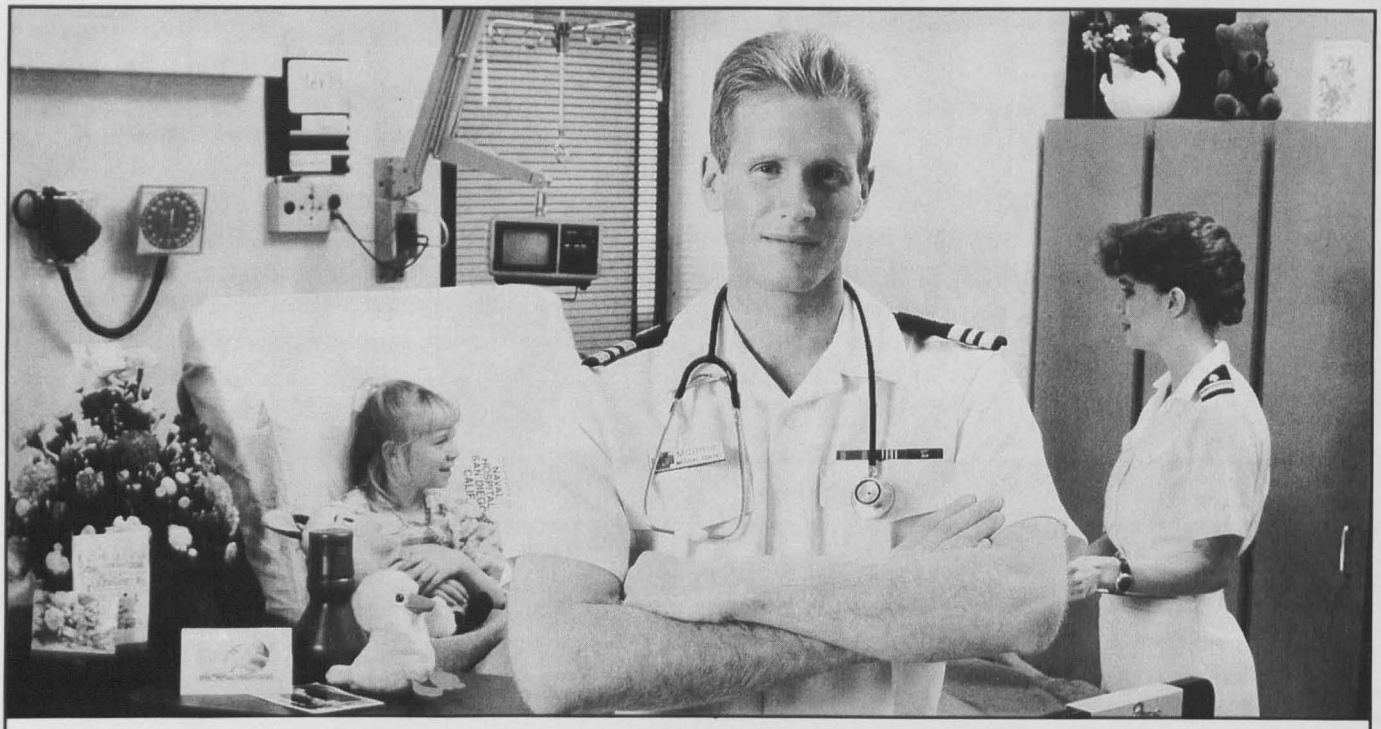

# A PRACTICE THAT OFFERS THE WORLD

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For more information, contact your local Navy Medical Programs officer, or if you'd like to talk to a Navy physician, call **1-800-USA-NAVY.** Ask for operator 10.

# NAVY

**YOU AND THE NAVY.**
**FULL SPEED AHEAD.**

**For bacterial vaginosis***

# MetroGel-Vaginal®
## (metronidazole vaginal gel)
## 0.75% Vaginal Gel

# The Clear Choice.

- **the #1 local therapy**[1]
- **efficacy equal to oral metronidazole**[2]
- **minimal side effects**
  - —low incidence of GI upset (3.4%)
  - —low incidence of nausea (2.0%)
  - —low incidence of metallic taste (1.7%)
- **minimal chance of alcohol interaction**
- **low incidence of yeast overgrowth (6.1%)**

Please see adjacent page for brief summary of prescribing information.

*Bacterial vaginosis formerly known as *Gardnerella* vaginitis, nonspecific vaginitis, *Haemophilus* vaginitis, anaerobic vaginosis, or *Corynebacterium* vaginitis.

**MetroGel-Vaginal®**
**Only 5 Day Therapy**

# MetroGel-Vaginal®
# (metronidazole vaginal gel)
# 0.75% Vaginal Gel

## #1 prescribed local therapy for BV[1]

### Efficacy equal to oral metronidazole[2]

In a direct comparative trial of 100 BV patients, MetroGel-Vaginal Therapy 5 days BID had efficacy rates equal to 7 days of oral metronidazole 500 mg BID.


### Only 5 Day Therapy

A clinical diagnosis of bacterial vaginosis is usually defined by the presence of a homogeneous vaginal discharge that (a) has a pH > 4.5, (b) emits a "fishy" amine odor when mixed with a 10% KOH solution, and (c) contains clue cells on microscopic examination. Gram's stain results consistent with a diagnosis of bacterial vaginosis include (a) markedly reduced or absent *Lactobacillus* morphology, (b) predominance of *Gardnerella* morphotype, and (c) absent or few white blood cells. Other pathogens commonly associated with vulvovaginitis, eg, *Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhoeae, Candida albicans*, and herpes simplex virus should be ruled out.

Brief Summary
Before prescribing please see full prescribing information.

## MetroGel-Vaginal®
### (metronidazole vaginal gel)
### 0.75% Vaginal Gel

FOR INTRAVAGINAL USE ONLY
NOT FOR OPHTHALMIC, DERMAL, OR ORAL USE

**DESCRIPTION:**
METROGEL-VAGINAL is formulated at pH 4.0. Each applicator full contains 37.5 mg of metronidazole.

**CLINICAL PHARMACOLOGY:**
Following a single, intravaginal 5-gram dose of metronidazole vaginal gel to 12 normal subjects, a mean maximum serum metronidazole concentration of 237 ng/mL was reported. This is approximately 2% of the mean maximum serum metronidazole concentration reported in the same subjects administered a single, oral 500-mg dose of metronidazole.

**INDICATIONS AND USAGE:**
METROGEL-VAGINAL is indicated in the treatment of bacterial vaginosis (formerly referred to as *Haemophilus* vaginitis, *Gardnerella* vaginitis, nonspecific vaginitis, *Corynebacterium* vaginitis or anaerobic vaginosis).

**NOTE:**
For purposes of this indication, a clinical diagnosis of bacterial vaginosis is usually defined by the presence of a homogeneous vaginal discharge that (a) has a pH of greater than 4.5, (b) emits a "fishy" amine odor when mixed with a 10% KOH solution and (c) contains clue cells on microscopic examination. Gram's stain results consistent with a diagnosis of bacterial vaginosis include (a) markedly reduced or absent *Lactobacillus* morphology, (b) predominance of *Gardnerella* morphotype and (c) absent or few white blood cells.

Other pathogens commonly associated with vulvovaginitis, e.g., *Trichomonas vaginalis, Chlamydia trachomatis, N. gonorrhoeae, Candida albicans* and *Herpes simplex* virus should be ruled out.

**CONTRAINDICATIONS:**
METROGEL-VAGINAL is contraindicated in patients with a prior history of hypersensitivity to metronidazole, parabens, other ingredients of the formulation or other nitroimidazole derivatives.

**WARNINGS:**
**Convulsive Seizures and Peripheral Neuropathy:** Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with oral metronidazole. The appearance of abnormal neurologic signs demands the prompt discontinuation of metronidazole vaginal gel therapy. Metronidazole vaginal gel should be administered with caution to patients with central nervous system diseases.

**Psychotic Reactions:** Psychotic reactions have been reported in alcoholic patients who were using oral metronidazole and disulfiram concurrently. Metronidazole vaginal gel should not be administered to patients who have taken disulfiram within the last two weeks.

**PRECAUTIONS:**
**General:** Patients with severe hepatic disease metabolize metronidazole slowly. Accordingly, for such patients, metronidazole vaginal gel should be administered cautiously. Known or previously unrecognized vaginal candidiasis may present more prominent symptoms during therapy with metronidazole vaginal gel.

Disulfiram-like reaction to alcohol has been reported with oral metronidazole, thus the possibility of such a reaction occurring while on metronidazole vaginal gel therapy cannot be excluded. METROGEL-VAGINAL contains ingredients that may cause burning and irritation of the eye.

**Drug Interactions:** Oral metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time.

**Drug/Laboratory Test Interactions:** Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT) alanine aminotransferase (ALT, SGPT) lactate dehydrogenase (LDH), triglycerides, and glucose hexokinase. Values of zero may be observed.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats but not in studies involving hamsters. These studies have not been conducted with 0.75% metronidazole vaginal gel, which would result in significantly lower systemic blood levels than those obtained with oral formulations.

Although metronidazole has shown mutagenic activity in a number of *in vitro* assay systems, studies in mammals *(in vivo)* have failed to demonstrate a potential for genetic damage.

Fertility studies have been performed in mice up to six times the recommended human vaginal dose (based on mg/m$^2$) and have revealed no evidence of impaired fertility.

**Pregnancy: Teratogenic Effects** Pregnancy Category B
There has been no experience to date with the use of METROGEL-VAGINAL in pregnant patients. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity or teratogenicity was observed when metronidazole was administered orally to pregnant mice at six times the recommended human vaginal dose (based on mg/m$^2$); however, in a single small study where the drug was administered intraperitoneally, some intrauterine deaths were observed. The relationship of these findings to the drug is unknown. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and because metronidazole is a carcinogen in rodents, this drug should be used during pregnancy only if clearly needed.

**Nursing Mothers:** Specific studies of metronidazole levels in human milk following intravaginally administered metronidazole have not been performed. However, metronidazole is secreted in human milk in concentrations similar to those found in plasma following oral administration of metronidazole. Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, 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:**
Adverse experiences reported in clinical trials involving 295 patients considered related, probably related or possibly related to METROGEL-VAGINAL were primarily genitourinary and gastrointestinal. Genitourinary reports were vaginal candidiasis (6.1%); vaginal, perineal or vulvar itching (1.4%); urinary frequency, vaginal or vulvar burning or irritation, vaginal discharge (not *Candida*) and vulvar swelling; each at an incidence of <1%. Gastrointestinal reports were cramps/pain (abdominal/uterine) (3.4%), nausea (2.0%), metallic or bad taste (1.7%) and constipation, decreased appetite and diarrhea, each at an incidence of <1%. Increased/decreased white blood cells (1.7%), dizziness, headache, lightheadedness and rash were noted, each at an incidence of <1%.

**Other metronidazole formulations:** Although lower systemic blood levels of metronidazole are seen compared to 500 mg of oral metronidazole, the possibility of adverse reactions like those seen with oral metronidazole cannot be excluded presently. Oral metronidazole has produced cardiovascular, central nervous system, gastrointestinal, genitourinary, hematopoietic, hypersensitivity and renal reactions.

**DOSAGE AND ADMINISTRATION:**
The recommended dose is one applicator full of METROGEL-VAGINAL (approximately 5 grams containing approximately 37.5 mg of metronidazole) intravaginally twice daily for 5 days. The medication should be applied once in the morning and once in the evening.

**HOW SUPPLIED:**
METROGEL-VAGINAL (metronidazole vaginal gel) is supplied in a 70 gram aluminum tube and packaged with a 5 gram vaginal applicator. NDC number is 55326-200-25.

**Caution: Federal law prohibits dispensing without a prescription.**

1 / 93

**REFERENCES:**


[1]MetroGel-Vaginal is prescribed more often than any other intravaginal bacterial vaginosis therapy. Oct. 1993 through present, National Prescription Audit of 20,000 Retail Pharmacies. IMS America, National Prescription Audit-NPA.

[2]McGregor JA, Hillier SL, Eschenbach DA, Kreutner AK, Galask RP. Efficacy of MetroGel-Vaginal versus oral metronidazole for treatment of bacterial vaginosis. A randomized, single-blind parallel comparison. Presented at International Society for STD Research; August 1995; New Orleans, LA.



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The American Board of Family Practice invites you to visit its Web site at *http://www.abfp.org*. The site includes the following topics:

- Requirements for residency training
- Requirements for certification
- Requirements for recertification
- Requirements for Certificates of Added Qualifications in Geriatric Medicine and Sports Medicine
- Future examination dates
- Information on ABFP publications including the *Journal of the American Board of Family Practice*, the *Directory of Diplomates*, and ABFP Reference Guides
- A listing of current and past members of the ABFP Board of Directors
- A staff listing and telephone directory
- The meaning of the ABFP emblem
- Official definitions and policies
- A brief history of the specialty
- Access by city and state to names of ABFP-Certified Family Physicians
- Access by city and state to names of ABFP-Certified Family Physicians with a Certificate of Added Qualifications in Geriatric Medicine
- Access by city and state to names of ABFP-Certified Family Physicians with a Certificate of Added Qualifications in Sports Medicine

We welcome your comments and suggestions.

**American Board of Family Practice Inc.**

2228 Young Drive
Lexington, Kentucky 40505

(606) 269-5626
FAX: (606) 266-9699

# ATTENTION

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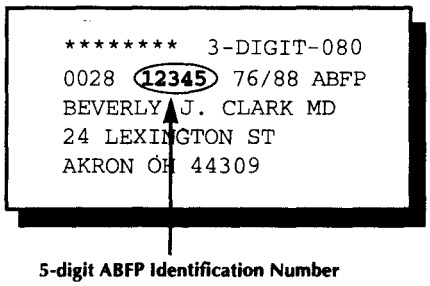


The Board prefers the use of *professional addresses,* because the address given will become your "address of record" with the Board and will be published in our Directory of Diplomates.

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

Name_____

| **Current Address** | **New Address** |
|---|---|
| Street_____ | Street _____ |
| _____ | _____ |
| City/State_____ | City/State_____ |
| Zip Code_____ | Zip Code_____ |

Effective Date of Change_____

Signature of Diplomate_____

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Year of Certification or Recertification_____

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**2228 Young Drive**
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The classified rate is $1.75 per word (minimum charge of $75.00 per ad insertion) and $100.00 per column inch for classified display ads.

Please call (609) 768-9360 and ask for classified advertising rate information on various classified display ad sizes. Prepayment in full is required with all classified advertising.

Confidential reply boxes are an additional $10.00 per insertion. Responses are sent directly every Tuesday and Thursday, and the box will remain open for three months.

**Note:** Our classified advertisements are all set in the same typeface and format. Italic, underlining or special typefaces are not available. All ads are listed by geographic location. Classified advertisements placed with JABFP are restricted to physician recruitment, faculty positions, CME courses, seminars, and practices for sale. All ads must relate to the medical field and are subject to approval.

Please refer to the schedule below for closing dates. All advertisements for employment must be nondiscriminatory and comply with all applicable laws and regulations. Ads that discriminate against applicants based on sex, age, race, religion, marital status or physical handicap will not be accepted.

**Classified Advertising Deadlines**

| Issue Date | Closing Date |
|---|---|
| May-June | April 1 |
| July-August | June 2 |
| September-October | August 1 |
| November-December | October 1 |
| January-February | December 1 |

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**Advertising Manager**
**MRA Publications, Inc.**
**2 Greenwich Office Park**
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## Northeast

**AMBULATORY FAMILY PRACTICE GROUP** in Harrisburg area seeking sixth physician to meet growing demand. Attractive salary and excellent benefits including retirement for BC/BE candidate. Call David Finney, Howe, Lawlor and Associates at 800-238-7150 or fax CV to 610-975-0574.

**NORTHWESTERN NEW JERSEY**—Practice opportunities with competitive compensation package available for BE/BC FAMILY PHYSICIANS. Send CV to: Elizabeth Lejeune, Northwest Covenant Medical Center, SSM Ambulatory Care Corporate Offices, 715 Route 10 East, Randolph, NJ 07869. Fax: 201-442-2330. Phone: 201-442-2307.

**SUBURBAN PITTSBURGH—FAMILY PRACTICE FACULTY**—An excellent opportunity exists for a BC Family Practitioner to become a member of a prestigious faculty group. This fully accredited program, which currently consists of 20 residents, is anticipating expansion. The program is sponsored by a progressive, midsized community hospital noted for its outstanding medical staff. Opportunity to live in a community that provides all of the benefits of a small town and an easy commute to a major metropolitan city. Enjoy award winning school districts, quality affordable housing and a vast array of cultural amenities. Excellent compensation/benefits. For more information, please contact: Elaine Bolanis at Daniel Stern & Associates; The Medical Center East; 211 N. Whitfield Street; Pittsburgh, PA 15206; Call 1-800-438-2476 or FAX 1-800-892-2781.

## Southeast

**JACKSON, TENNESSEE: Open rank, full-time faculty.** The University of Tennessee Jackson—Madison County General Hospital Family Medicine Residency Program is seeking faculty. Candidates should be residency trained, ABFP certified MD or DO physicians that qualify for an unrestricted Tennessee medical license. Must have skills to qualify for normal deliveries. ATLS, ACLS, and AAFP preferred. Tenure track or clinical track with opportunities in teaching, patient care, scholarship and faculty development. Salary and academic appointment commensurate with training and experience. Interested candidates should send a CV including personal goals to David E. Roberts, M.D., Program Director; UT Family Medicine; 294 Summar Drive; Jackson, TN 38301. The University of Tennessee is an Equal Opportunity/Affirmative Action/Title VI/Title IX/Section 504/ADA employer.

**SOUTH CAROLINA:** Graduating residents and experienced practitioners are invited to contact Dr. Chermol at 800-866-6045 to discuss exceptional practice opportunities. City of 50,000; superb location between two major cities and the mountains and beaches. Salaried and private practice positions available.

**DEAN, COLLEGE OF COMMUNITY HEALTH SCIENCES AND ASSOCIATE DEAN, UNIVERSITY OF ALABAMA SCHOOL OF MEDICINE, TUSCALOOSA PROGRAM.** The University of Alabama School of Medicine is seeking nominations and applications for the position of Dean, College of Community Health Sciences/Associate Dean, University of Alabama School of Medicine—Tuscaloosa Program. The medical program is a branch campus of the medical school in Birmingham. It is responsible for the medical education of third and fourth year medical students. The college includes a large, well known Family Practice program that is supported by both the University and DCH Regional Medical Center, a 600+ bed regional referral center. The successful candidate will have a terminal degree (MD or PhD or equivalent) and, if an MD, be board certified in a specialty, preferably in a primary care specialty. The candidate must be committed to high quality medical education and related fields in a manner compatible with the aims, goals and mission of the medical school and the university. Research in health care delivery systems, outcome studies, rural issues and medical education is preferred. Administrative experience in a medical school, preferably one with an evolving matrix organization and multiple campuses is desirable.

Other related colleges and schools of The University of Alabama include: School of Social Work, Nursing, Human Environmental Sciences, Education, and Arts and Sciences. The University of Alabama, the state's oldest public university and the senior comprehensive doctoral level institution in Alabama, is located in Tuscaloosa, a metropolitan area of approximately 100,000 with a vibrant economy, moderate climate, and a reputation across the South as an innovative, progressive community with a high quality of life. For further information or to make nominations or application, please send curriculum vitae to: Amy Thompson, Director, Administrative Services, Medical Dean's Office-MEB 310, University of Alabama School of Medicine, Birmingham, AL 35294-3293, Telephone 205-934-1111, Fax 205-934-0333. The University of Alabama is an Equal Opportunity/Affirmative Action Employer.

## Midwest

**CHICAGO, teaching & practice opportunities:** Board-certified Family practitioners are needed for part-time or full-time positions in one of the oldest and largest FP residency training programs in the country—in the Department of Family Practice at Cook County Hospital. Join this dynamic group of family practitioners who are committed to training FPs to care for the medically underserved in a program proud of its tradition of cultural diversity and commitment to the underserved. Practice opportunities for physicians seeking to practice the full scope of family medicine (including OB) are available at the soon to expand Dr. Jorge Prieto HC in the South Lawndale community and at the Englewood Clinic in that community. Full- and part-time faculty positions also available. Competitive salary, good benefits package.

Training available for new teachers in the well-known Faculty Development Center to develop skills in education, policy, and research. If interested, contact Carolyn Lopez, MD, Chair, Department of Family Practice, Cook County Hospital, 1900 West Polk Street, Chicago 60612 or 312-633-8587.

**SEEKING FULL TIME BC/BE FAMILY PHYSICIAN.** To supervise quality primary patient care while teaching in a highly respected family practice residency program. OB experience preferred. Dept. of Community and Family Medicine—University of Missouri-Kansas City. Contact with current CV: Paul A. Williams, M.D., Chairman, Truman Medical Center-East, 7900 Lee's Summit Road, Kansas City, MO 64139, 816-373-4485 x 1021, e-mail address: paulawms@qni.com.

**AHEC - FORT SMITH, ARKANSAS** is recruiting a family physician for a full-time faculty position. Community-based, university-administered 6-6-6 Program in community of 75,000 in scenic Arkansas river valley near Ozark and Ouachita Mountains. Temperate climate with four seasons. Duties include teaching residents and medical students and direct patient care including operative OB. Competitive salary with excellent benefit package. Must be ABFP certified and able to obtain an Arkansas license. Call 501-785-2431 for Larry L. Hanley, M.D., Program Director or L.C. Price, M.D., AHEC Director, or send CV to 612 So.12th St., Fort Smith, AR 72901-4702. EOE.



**MOTION PICTURE AND TV FUND**—Primary Care Physicians (Family Practice or Internal Medicine) wanted for Health Centers located Toluca Lake (Burbank), California. BC a must with a minimum of three years of outpatient experience in a managed care setting. Salary plus bonus, paid malpractice, CME time and expenses. Call is "phone" only (2 weeks per year). CONTACT: Sharon Tanabe 310-843-4179 or FAX CV to 310-553-6452.

**NATIVIDAD MEDICAL CENTER FAMILY PRACTICE RESIDENCY** is a 21-resident program at the County Hospital of Monterey in Salinas, California. The Family Practice Residency is the only residency at the hospital. We will have an opening in the second year class beginning July, 1997. Interested applicants should forward a CV to: Richard Brunader, M.D., Program Director, Family Practice Residency, Natividad Medical Center, 1330 Natividad Road, Salinas, CA 93906; 408-755-4201. AA/EOE/M/F/H.

**PROFESSIONAL OPPORTUNITIES**

**SEATTLE/PUGET SOUND AREA**—Successful family practice for sale. Clinic specializes in women's health care in affluent suburb 10 miles east of Seattle. Opportunity to form group practice, and also to join prestigious teaching/research oriented hospitals in Seattle and on the eastside. Call/write J. Buchanan, 2300 88th Ave NE, Bellevue, WA 98004 (206-453-9381), or e-mail kbuchan@aol.com.

First-line therapy option

# ZIAC®

(bisoprolol fumarate-hydrochlorothiazide)
2.5, 5, & 10 mg Tablets with 6.25 mg HCTZ

**Hardworking therapy** patients hardly notice

**References: 1.** DeQuattro V, Weir MR. Bisoprolol fumarate/hydrochlorothiazide 6.25 mg: a new low-dose option for first-line antihypertensive therapy. *Adv Ther.* 1993;10:197-206. **2.** Zachariah PK, Messerli FH, Mroczek W. Low-dose bisoprolol/hydrochlorothiazide: an option in first-line, antihypertensive treatment. *Clin Ther.* 1993;15:779-787. **3.** Prisant LM, Weir MR, Papademetriou V, et al. Low-dose drug combination therapy: an alternative first-line approach to hypertension treatment. *Am Heart J.* 1995;130:359-366. **4.** Data on file. Lederle Laboratories, Pearl River, NY.

## Brief Summary

### ZIAC® (Bisoprolol Fumarate and Hydrochlorothiazide) Tablets

FOR FULL PRESCRIBING INFORMATION, PLEASE CONSULT PACKAGE INSERT.

### DESCRIPTION

ZIAC (bisoprolol fumarate and hydrochlorothiazide) is indicated for the treatment of hypertension. It combines two antihypertensive agents in a once-daily dosage: a synthetic beta$_1$-selective (cardioselective) adrenoceptor blocking agent (bisoprolol fumarate) and a benzothiadiazine diuretic (hydrochlorothiazide).

### CLINICAL PHARMACOLOGY

At doses ≥ 20 mg bisoprolol fumarate inhibits beta$_1$-adrenoreceptors located in bronchial and vascular musculature. To retain relative selectivity, it is important to use the lowest effective dose.

### CONTRAINDICATIONS

Cardiogenic shock, overt cardiac failure (see **WARNINGS**), second- or third-degree AV block, marked sinus bradycardia, anuria, and hypersensitivity to either component of this product or to other sulfonamide-derived drugs.

### WARNINGS

**Cardiac Failure:** Beta-blocking agents should be avoided in patients with overt congestive failure.
**Patients Without a History of Cardiac Failure:** Continued depression of the myocardium with beta-blockers can precipitate cardiac failure. At the first signs or symptoms of heart failure, discontinuation of ZIAC should be considered.
**Abrupt Cessation of Therapy:** Abrupt cessation of beta-blockers should be avoided. Even in patients without overt coronary artery disease, it may be advisable to taper therapy with ZIAC over approximately 1 week with the patient under careful observation. If withdrawal symptoms occur, beta-blocking agent therapy should be reinstituted, at least temporarily.
**Peripheral Vascular Disease:** Beta-blockers should be used with caution in patients with peripheral vascular disease.
**Bronchospastic Disease: PATIENTS WITH BRONCHOSPASTIC PULMONARY DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS.**
**Anesthesia and Major Surgery:** If used perioperatively, particular care should be taken when anesthetic agents that depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used.
**Diabetes and Hypoglycemia:** Beta-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned. Also, latent diabetes mellitus may become manifest and diabetic patients given thiazides may require adjustment of their insulin dose.
**Thyrotoxicosis:** Beta-adrenergic blockade may mask clinical signs of hyperthyroidism. Abrupt withdrawal of beta-blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate thyroid storm.
**Renal Disease:** Cumulative effects of the thiazides may develop in patients with impaired renal function. In such patients, thiazides may precipitate azotemia. In subjects with creatinine clearance less than 40 mL/min, the plasma half-life of bisoprolol fumarate is increased up to threefold, as compared to healthy subjects.
**Hepatic Disease:** ZIAC should be used with caution in patients with impaired hepatic function or progressive liver disease.

### PRECAUTIONS

**General:** *Electrolyte and Fluid Balance Status:* Periodic determination of serum electrolytes should be performed, and patients should be observed for signs of fluid or electrolyte disturbances. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Hypokalemia may develop. Hypokalemia and hypomagnesemia can provoke ventricular arrhythmias or sensitize or exaggerate the response of the heart to the toxic effects of digitalis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

*Parathyroid Disease:* Calcium excretion is decreased by thiazides, and pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy.

*Hyperuricemia:* Hyperuricemia or acute gout may be precipitated in certain patients receiving thiazide diuretics. Bisoprolol fumarate, alone or in combination with HCTZ, has been associated with increases in uric acid.
**Drug Interactions:** ZIAC may potentiate the action of other antihypertensive agents used concomitantly. ZIAC should not be combined with other beta-blocking agents. In patients receiving concurrent therapy with clonidine, if therapy is to be discontinued, it is suggested that ZIAC be discontinued for several days before the withdrawal of clonidine.

ZIAC should be used with caution when myocardial depressants or inhibitors of AV conduction or antiarrhythmic agents are used concurrently.

*Bisoprolol Fumarate:* Concurrent use of rifampin increases the metabolic clearance of bisoprolol fumarate, shortening its elimination half-life. Pharmacokinetic studies document no clinically relevant interactions with other agents given concomitantly, including thiazide diuretics, digoxin and cimetidine. There was no effect of bisoprolol fumarate on prothrombin times in patients on stable doses of warfarin.

Risk of Anaphylactic Reaction: While taking beta-blockers, patients with a history of severe anaphylactic reaction may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic and may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

*Hydrochlorothiazide:* The following drugs may interact with thiazide diuretics. Alcohol, barbiturates, or narcotics — potentiation of orthostatic hypotension may occur. Dosage adjustment of the antidiabetic drugs (oral agents and insulin) may be required. Other antihypertensive drugs — additive effect or potentiation. Cholestyramine and colestipol resins — single doses of cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption in the gastrointestinal tract by up to 85 percent and 43 percent, respectively. Corticosteroids, ACTH — intensified electrolyte depletion, particularly hypokalemia. Possible decreased response to pressor amines but not sufficient to preclude their use. Possible increased responsiveness to muscle relaxants, nondepolarizing. Generally, lithium should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. The administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. Photosensitivity reactions and possible exacerbation or activation of systemic lupus erythematosus have been reported in patients receiving thiazides. The antihypertensive effects of thiazides may be enhanced in the post-sympathectomy patient.
**Laboratory Test Interactions:** Based on reports involving thiazides, ZIAC may decrease serum levels of protein-bound iodine without signs of thyroid disturbance. Because it includes a thiazide, ZIAC should be discontinued before carrying out tests for parathyroid function (see **PRECAUTIONS**–*Parathyroid Disease*).

### ADVERSE REACTIONS

**ZIAC:** Bisoprolol fumarate/H6.25 mg is well tolerated in most patients. Most adverse effects (AEs) have been mild and transient. In more than 65,000 patients treated worldwide with bisoprolol fumarate, occurrences of bronchospasm have been rare. Discontinuation rates for AEs were similar for B/H6.25 mg and placebo-treated patients.

In the United States, 252 patients received bisoprolol fumarate (2.5, 5, 10, or 40 mg)/H6.25 mg and 144 patients received placebo in two controlled trials. In Study 1, bisoprolol fumarate 5/H6.25 mg was administered for 4 weeks. In Study 2, bisoprolol fumarate 2.5, 10 or 40/H6.25 mg was administered for 12 weeks. All adverse experiences, whether drug-related or not, and drug-related adverse experiences in patients treated with B2.5-10/H6.25 mg, reported during comparable, 4 week treatment periods by at least 2% of bisoprolol fumarate/H6.25 mg-treated patients (plus additional selected adverse experiences) are presented in the following table:

**ZIAC® (Bisoprolol Fumarate and Hydrochlorothiazide) Tablets**

| Body System/ Adverse Experience | % of Patients with Adverse Experiences* | | | |
|---|---|---|---|---|
| | All Adverse Experiences | | Drug-Related Adverse Experiences | |
| | Placebo† (n = 144) % | B2.5-40/H6.25† (n = 252) % | Placebo† (n = 144) % | B2.5-10/H6.25† (n = 221) % |
| Cardiovascular | | | | |
| bradycardia | 0.7 | 1.1 | 0.7 | 0.9 |
| arrhythmia | 1.4 | 0.4 | 0.0 | 0.0 |
| peripheral ischemia | 0.9 | 0.7 | 0.9 | 0.4 |
| chest pain | 0.7 | 1.8 | 0.7 | 0.9 |
| Respiratory | | | | |
| bronchospasm | 0.0 | 0.0 | 0.0 | 0.0 |
| cough | 1.0 | 2.2 | 0.7 | 1.5 |
| rhinitis | 2.0 | 0.7 | 0.7 | 0.9 |
| URI | 2.3 | 2.1 | 0.0 | 0.0 |
| Body as a Whole | | | | |
| asthenia | 0.0 | 0.0 | 0.0 | 0.0 |
| fatigue | 2.7 | 4.6 | 1.7 | 3.0 |
| peripheral edema | 0.7 | 1.1 | 0.7 | 0.9 |
| Central Nervous System | | | | |
| dizziness | 1.8 | 5.1 | 1.8 | 3.2 |
| headache | 4.7 | 4.5 | 2.7 | 0.4 |
| Musculoskeletal | | | | |
| muscle cramps | 0.7 | 1.2 | 0.7 | 1.1 |
| myalgia | 1.4 | 2.4 | 0.0 | 0.0 |
| Psychiatric | | | | |
| insomnia | 2.4 | 1.1 | 2.0 | 1.2 |
| somnolence | 0.7 | 1.1 | 0.7 | 0.9 |
| loss of libido | 1.2 | 0.4 | 1.2 | 0.4 |
| impotence | 0.7 | 1.1 | 0.7 | 1.1 |
| Gastrointestinal | | | | |
| diarrhea | 1.4 | 4.3 | 1.2 | 1.1 |
| nausea | 0.9 | 1.1 | 0.9 | 0.9 |
| dyspepsia | 0.7 | 1.2 | 0.7 | 0.9 |

* Averages adjusted to combine across studies.
† Combined across studies.

Other adverse experiences that have been reported with the individual components are listed below.
**Bisoprolol Fumarate:** In clinical trials worldwide, a variety of other AEs, in addition to those listed above, have been reported. While in many cases it is not known whether a causal relationship exists between bisoprolol and these AEs, they are listed to alert the physician to a possible relationship. *Central Nervous System:* Unsteadiness, vertigo, syncope, paresthesia, hyperesthesia, sleep disturbance/vivid dreams, depression, anxiety/restlessness, decreased concentration/memory. *Cardiovascular:* Palpitations and other rhythm disturbances, cold extremities, claudication, hypotension, orthostatic hypotension, chest pain, congestive heart failure. *Gastrointestinal:* Gastric/epigastric/abdominal pain, peptic ulcer, gastritis, vomiting, constipation, dry mouth. *Musculoskeletal:* Arthralgia, muscle/joint pain, back/neck pain, twitching/tremor. *Skin:* Rash, acne, eczema, psoriasis, skin irritation, pruritus, purpura, flushing, sweating, alopecia, dermatitis, exfoliative dermatitis (very rarely), cutaneous vasculitis. *Special Senses:* Visual disturbances, ocular pain/pressure, abnormal lacrimation, tinnitus, decreased hearing, earache, taste abnormalities. *Metabolic:* Gout. *Respiratory:* Asthma, bronchitis, dyspnea, pharyngitis, sinusitis. *Genitourinary:* Peyronie's disease (very rarely), cystitis, renal colic, polyuria. *General:* Malaise, edema, weight gain, angioedema.

In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects: *Central Nervous System:* Reversible mental depression progressing to catatonia, hallucinations, an acute reversible syndrome characterized by disorientation to time and place, emotional lability, slightly clouded sensorium. *Allergic:* Fever, combined with aching and sore throat, laryngospasm, and respiratory distress. *Hematologic:* Agranulocytosis, thrombocytopenia. *Gastrointestinal:* Mesenteric arterial thrombosis and ischemic colitis. *Miscellaneous:* The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with bisoprolol fumarate during investigational use or extensive foreign marketing experience.
**Hydrochlorothiazide:** The following adverse experiences, in addition to those listed in the above table, have been reported with hydrochlorothiazide (generally with doses of 25 mg or greater). *General:* Weakness. *Central Nervous System:* Vertigo, paresthesia, restlessness. *Cardiovascular:* Orthostatic hypotension (may be potentiated by alcohol, barbiturates, or narcotics). *Gastrointestinal:* Anorexia, gastric irritation, cramping, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, cholecystitis, sialadenitis, dry mouth. *Musculoskeletal:* Muscle spasm. *Hypersensitive Reactions:* Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions. *Special Senses:* Transient blurred vision, xanthopsia. *Metabolic:* Gout. *Genitourinary:* Sexual dysfunction, renal failure, renal dysfunction, interstitial nephritis.

### LABORATORY ABNORMALITIES

**ZIAC:** Because of the low dose of hydrochlorothiazide in ZIAC, adverse metabolic effects with B/H6.25 mg are less frequent and of smaller magnitude than with HCTZ 25 mg.

Treatment with both beta-blockers and thiazide diuretics is associated with increases in uric acid. Mean increases in serum triglycerides were observed in patients treated with bisoprolol fumarate and hydrochlorothiazide 6.25 mg. Total cholesterol was generally unaffected, but small decreases in HDL cholesterol were noted.

Other laboratory abnormalities that have been reported with the individual components are listed below.
**Bisoprolol Fumarate:** In clinical trials, the most frequently reported laboratory change was an increase in serum triglycerides, but this was not a consistent finding.

Sporadic liver test abnormalities have been reported. In the U.S. controlled trials experience with bisoprolol fumarate treatment for 4 to 12 weeks, the incidence of concomitant elevations in SGOT and SGPT of between 1 to 2 times normal was 3.9%, compared to 2.5% for placebo. No patient had concomitant elevations greater than twice normal.

In the long-term, uncontrolled experience with bisoprolol fumarate treatment for 6 to 18 months, the incidence of one or more concomitant elevations in SGOT and SGPT of between 1-2 times normal was 6.2%. The incidence of multiple occurrence was 1.9%. For concomitant elevations in SGOT and SGPT of greater than twice normal, the incidence was 1.5%. The incidence of multiple occurrences was 0.3%. In many cases these elevations were attributed to underlying disorders, or resolved during continued treatment with bisoprolol fumarate.

Other laboratory changes included small increases in uric acid, creatinine, BUN, serum potassium, glucose, and phosphorus and decreases in WBC and platelets. There have been occasional reports of eosinophilia. These were generally not of clinical importance and rarely resulted in discontinuation of bisoprolol fumarate.

As with other beta-blockers, ANA conversions have also been reported on bisoprolol fumarate. About 15% of patients in long-term studies converted to a positive titer, although about one-third of these patients subsequently reconverted to a negative titer while on continued therapy.
**Hydrochlorothiazide:** Hyperglycemia, glycosuria, hyperuricemia, hypokalemia and other electrolyte imbalances (see **PRECAUTIONS**), hyperlipidemia, hypercalcemia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, and hemolytic anemia have been associated with HCTZ therapy.

See **DOSAGE AND ADMINISTRATION** section in package insert for complete dosing and precautionary information.

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