The Journal of the American Board of Family Practice

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Classified Advertising Deadlines

Issue Date	Closing Date
March-April	February 1
May-June	April 1
July-August	June 1
September-October	August 1
November-December	October 3

Northeast

FAMILY PRACTICE—SOUTHWESTERN PENNSYLVANIA—Four Board Certified physicians seek BE/BC associate for well-established and expanding practice. Enjoy working in a large, modern office with lab and x-ray capabilities. Live in a community which provides quality, affordable housing, excellent schools and easy access to Pittsburgh's sports and cultural amenities. Excellent compensation/benefit package. For more information, please call Elaine Bolanis at Daniel Stern and Associates at 1-800-438-2476 or FAX 1-800-892-2781.

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Southeast

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Available July 1, 1997, in an established ACGME accredited geriatric fellowship program. Two one-year positions available. Strong clinical component. Faculty development including research design, pedagogic skills; curriculum design/evaluation and administrative development.

Apply to: Kenneth Steinweg, MD, Department of Family Medicine, Brody 4N-72, EAST CAROLINA UNIVERSITY SCHOOL OF MEDICINE, Greenville, NC 27858-4354. East Carolina is an Equal Opportunity/Affirmative Action Employer. Applicants must comply with the Immigration Reform and Control Act. We Accommodate Individuals With Disabilities.

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; non-competitive environment; superb location between two major cities and the mountains and beaches.

Midwest

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.

CINCINNATI, OHIO
BC/BE INTERNISTS or FAMILY PRACTITIONERS

Deaconess Associations, Inc., based in Cincinnati, Ohio, has several practice opportunities for BC/BE Internists or Family Practitioners. The practices are owned and operated by Deaconess Hospital. Opportunities are uniquely designed to match physician and patient base needs. Competitive salary, full benefits, call coverage, and no financial risk. One physician group opportunity features outpatient work only. For additional information contact Kathy Kraushar, Deaconess Hospital, 311 Straight Street, Cincinnati, Ohio 45219, (513) 559-2601. FAX: (513) 475-5251.

BC/FAMILY PRACTICE PHYSICIAN—Liberty Healthcare Corp. seeks a qualified physician for our ambulatory care setting NW of Des Moines, IA. You will be providing primary care to employees/dependents of a major corporation. Grow into a leadership role in a premier practice setting. Excellent compensation, generous paid time off, stable 40-hour, Mon-Fri schedule. Contact Connie Grazel, Liberty Healthcare Corporation, 401 City Ave., Suite 820, Bala Cynwyd, PA 19004; 800-331-7122; 24-hour line 610-617-3699, ext. 157; fax 610-667-5559. EOE.

WESTERN WISCONSIN—Join one of our nation's largest multispecialty groups (medical staff of 315) offering family practice opportunities in several surrounding regional clinics in Western Wisconsin and Northern Iowa. Family Medicine is the organization's single largest department, with 35 physicians. Provide quality care with other family physicians in fully equipped facilities. Consultants visit branch sites on a regularly scheduled basis. 92 subspecialists are also easily accessible via Med-Link service. All clinic sites are located in attractive communities within driving distance of other major urban areas. Excellent quality of life, year round spectacular outdoor recreational opportunities, gorgeous sightseeing. Competitive salary and benefit package. For more information call Jackie Laske at (800) 243-4353.

Southwest

BC/BE PHYSICIAN: 2 busy Family Practitioners in Dallas looking for BC/BE physician in a busy practice located near a tertiary care hospital. Will guarantee a competitive salary and help with practice set-up and management. Dallas abounds with cultural activities, all major league sports, golf courses, lakes, and museums. Respond by mail to T. Dale Ragle, MD, 8230 Walnut Hill, Suite 600, Dallas, TX 75231. Phone: (214) 361-0946, ext. 22. Fax: (214) 373-7030. E-Mail-Dragle@ix.netcom.com.

West

FELLOWSHIP IN RURAL FAMILY MEDICINE

Tacoma Family Medicine (TFM) announces openings for August 1, 1997 in our Fellowship in Rural Family Medicine. TFM, an 18-year-old Family Practice Residency affiliated with the University of Washington, has a strong history of training physicians for rural practice. We are currently in the 7th year of our Fellowship in Rural Family Medicine and 5 Fellows are currently participating in the program. It is anticipated that the Rural Fellowship will accept 5 physicians for the year beginning August 1, 1997. The curriculum will consist of 6 months of intensive training in high-risk and operative obstetrics and 6 months of electives tailored to the needs of the individual. Options for the individually tailored time include adult and pediatric critical care, all medical and surgical specialties, emergency services, public health, practice management, etc. As the only civilian residency in Tacoma, WA, located on beautiful Puget Sound, this is an ideal training site. Contact David Acosta, M.D., Program Director, Tacoma Family Medicine, 521 Martin Luther King Jr. Way Street, Tacoma, WA 98405 for details. Applicants should be finishing a Family Practice Residency in 1997 or have previously completed residency training in Family Medicine and have an interest in rural practice.

1997 Seoul WONCA Asia Pacific Regional Conference

1997 서울 세계가정의학회 아시아 태평양 지역회의

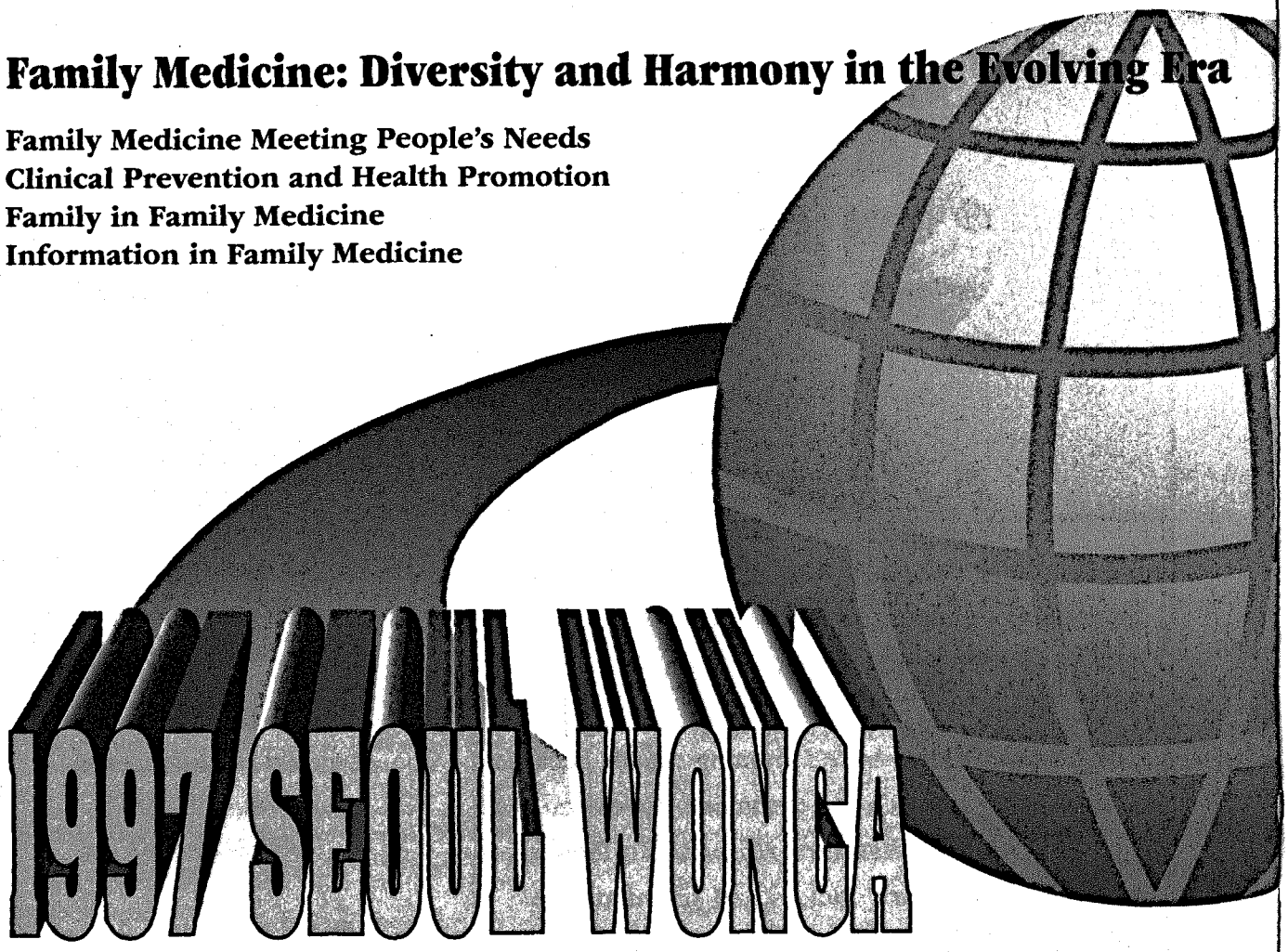
가정의학 새로운 시대의 다양성과 조화

The World Organization of Family Doctors
August 30-September 3, 1997
Sheraton Walker Hill Hotel & Towers
Seoul, Korea

Call for Abstracts: By Feb 28, 1997
Preregistration: By Jun 30, 1997

Family Medicine: Diversity and Harmony in the Evolving Era

Family Medicine Meeting People's Needs
Clinical Prevention and Health Promotion
Family in Family Medicine
Information in Family Medicine



Aug 27-29	WONCA Council Meeting
Aug 30	WONCA AP Regional Council Meeting
Aug 30	WONCA AP Working Party
Aug 30	WONCA AP Journal Editor's Guild
Aug 30	WONCA Research Network Meeting
Aug 30	WONCA Working Party on Informatics Meeting
Aug 31-Sept 3	WONCA AP Regional Conference
Sept 4-6	WONCA FM Education Workshop

Hosted by
The Korean Academy of Family Medicine

Conference Secretariat
SL Kangnam PO Box 305,
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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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