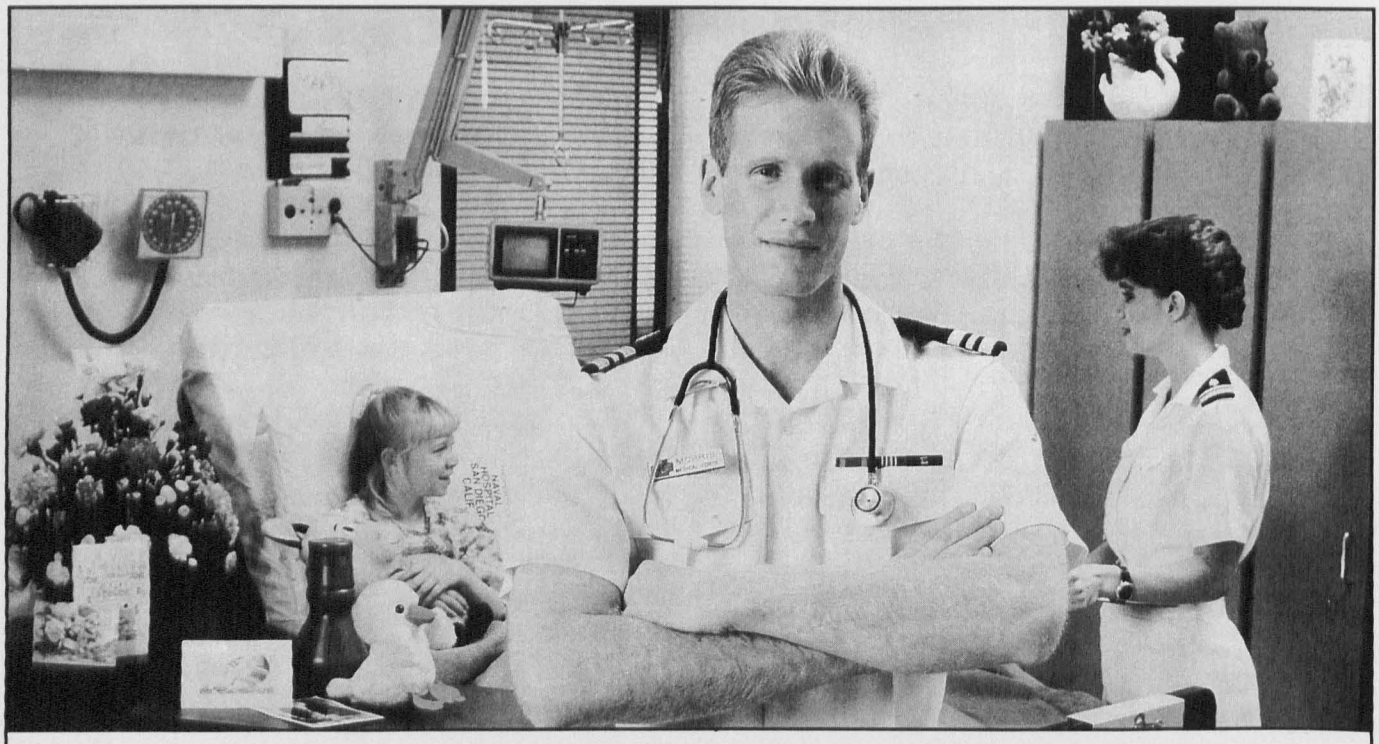

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**References: 1.** Neutel JM, Rolf CN, Valentine SN, et al. Low-dose combination therapy as first line treatment of mild-to-moderate hypertension. *Cardiovasc Rev Rep.* 1996;17:33-45. **2.** Zachariah PK, Messerli FH, Mroczek W. Low-dose bisoprolol/hydrochlorothiazide: 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.** 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.

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**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,-selective (cardioselective) adrenoceptor blocking agent (bisoprolol fumarate) and a benzothiadiazine diuretic (hydrochlorothiazide).

**CLINICAL PHARMACOLOGY**

At doses ≥ 20 mg bisoprolol fumarate inhibits beta,-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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