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[1]*

ZIAC controls mild-to-moderate hypertension in up to 80% of patients[1†]

ZIAC controls blood pressure for a full 24 hours for true once-a-day dosing[2]

ZIAC minimizes traditional beta-blocker- and HCTZ-associated metabolic effects (hypokalemia, hyperuricemia, hypercholesterolemia, hyperglycemia)[1]

*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.

First-line therapy option

ZIAC™

(bisoprolol fumarate-hydrochlorothiazide)

2.5, 5, & 10 mg Tablets with 6.25 mg HCTZ

First-line therapy option

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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. Lewin AJ, Lueg MC, Targum S, et al. A clinical trial evaluating the 24-hour effects of bisoprolol/hydrochlorothiazide 5 mg/6.25 mg combination in patients with mild to moderate hypertension. *Clin Cardiol.* 1993;16:732-736.

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.

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 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). *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 6-18 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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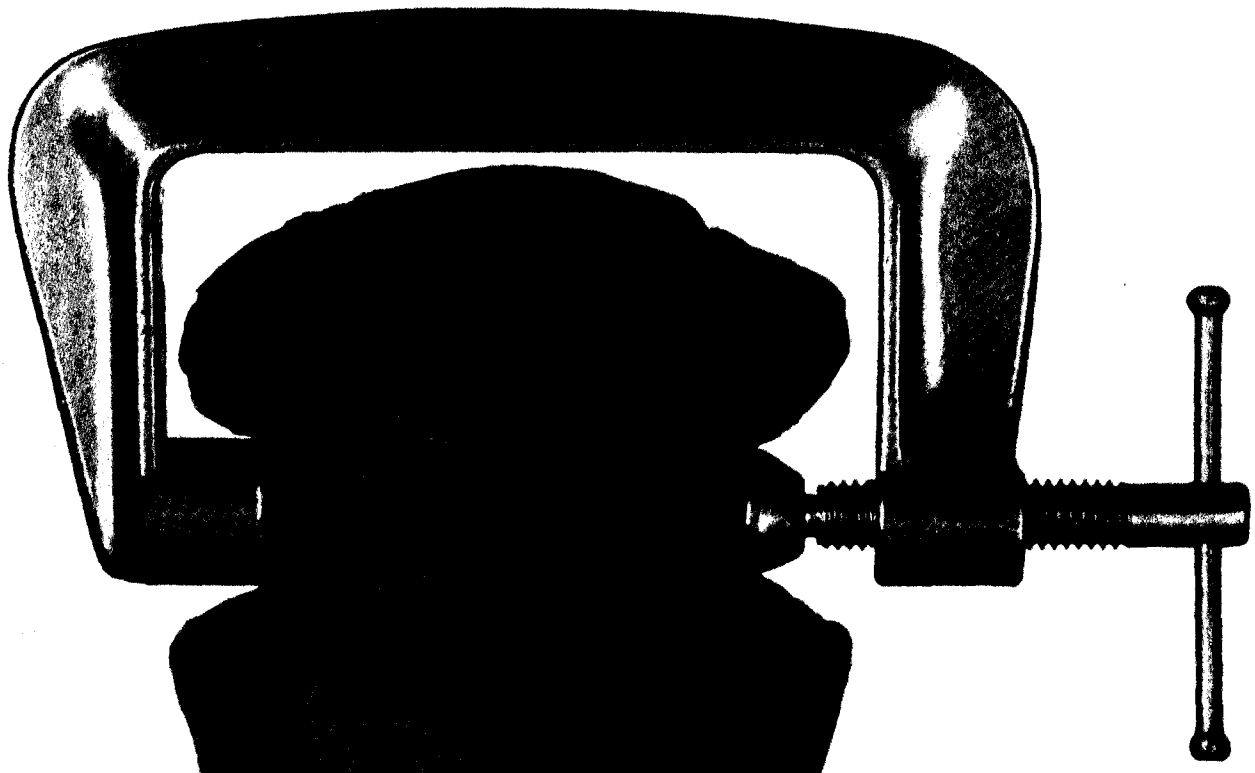

Non-scheduled* **Esgic plus tablets**

Butalbital 50mg **(Warning: May be habit forming)**
/Acetaminophen 500mg/Caffeine 40mg

Over 50% more analgesic power than the leading products in its class.

Well tolerated — Without aspirin-related side effects such as GI irritation and GI bleeding.[1-5] The most frequent adverse reactions are drowsiness and dizziness.

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Please see references and brief summary of full prescribing information on adjacent page.

*In most states.

Esgic*plus*™ tablets

Butalbital 50mg **(Warning: May be habit forming)**
/Acetaminophen 500mg/Caffeine 40mg

References: 1. Benson GD. Hepatotoxicity following the therapeutic use of antipyretic analgesics. *Am J Med.* 1983;75(suppl 5A):85-93. **2.** Jick H. Effects of aspirin and acetaminophen in gastro-intestinal hemorrhage. *Arch Intern Med.* 1981;141:316-321. **3.** Mielke CH Jr. Comparative effects of aspirin and acetaminophen on hemostasis. *Arch Intern Med.* 1981;141:305-310. **4.** Hansten PD. *Drug Interactions.* 5th ed. Philadelphia, PA: Lea & Febiger; 1985, p. 95. **5.** Insel PA. Analgesic-antipyretics and antiinflammatory agents; drugs employed in the treatment of rheumatoid arthritis and gout. In: Gilman AG, Rall TW, Nies AS, Taylor P, eds. *The Pharmacological Basis of Therapeutics.* 8th ed. New York, NY: Pergamon Press; 1990:638-681.

ESGIC-PLUS™ Tablets

(Butalbital, Acetaminophen and Caffeine Tablets, USP)
50mg/500mg/40mg

Brief Prescribing Information: (Please see package insert for full prescribing information) Each Esgic-plus™ Tablet contains: Butalbital, USP 50 mg. WARNING: May be habit forming. Acetaminophen, USP 500 mg, Caffeine, USP 40 mg. In addition each tablet contains the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide and stearic acid.

CONTRAINDICATIONS: This product is contraindicated under the following conditions: • Hypersensitivity or intolerance to any component of this product. • Patients with porphyria. **WARNINGS:** Butalbital is habit-forming and potentially abusable. Consequently, the extended use of this product is not recommended.

PRECAUTIONS: General: Esgic-plus™ Tablets should be prescribed with caution in certain special-risk patients, such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, or acute abdominal conditions. **Information for Patients:** This product may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking this product. Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided. Butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed. **Laboratory Tests:** In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests. **Drug Interactions:** The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors. Esgic-plus™ Tablets may enhance the effects of: other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression. **Drug/Laboratory Test Interactions:** Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No adequate studies have been conducted in animals to determine whether acetaminophen or butalbital have a potential for carcinogenesis, mutagenesis, or impairment of fertility. **Pregnancy:** *Teratogenic Effects:* Pregnancy Category C: Animal reproduction studies have not been conducted with this combination product. It is also not known whether Esgic-plus™ Tablets can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. This product should be given to a pregnant woman only when clearly needed. *Nonteratogenic Effects:* Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last two months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5 mg/kg, which was tapered without further seizure or other withdrawal symptoms. **Nursing Mothers:** Caffeine, barbiturates and acetaminophen are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from Esgic-plus™ Tablets, 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 below the age of 12 have not been established.

ADVERSE REACTIONS: Frequently Observed: The most frequently reported adverse reactions are drowsiness, light-headedness, dizziness, sedation, shortness of breath, nausea, vomiting, abdominal pain, and intoxicated feeling. **Infrequently Observed:** All adverse events tabulated below are classified as infrequent. *Central Nervous:* headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, sluggishness, seizure. Mental confusion, excitement or depression can also occur due to intolerance, particularly in elderly or debilitated patients, or due to overdosage of butalbital. *Autonomic Nervous:* dry mouth, hyperhidrosis. *Gastrointestinal:* difficulty swallowing, heartburn, flatulence, constipation. *Cardiovascular:* tachycardia. *Musculoskeletal:* leg pain, muscle fatigue. *Genitourinary:* diuresis. *Miscellaneous:* pruritus, fever, earache, nasal congestion, tinnitus, euphoria, allergic reactions. Several cases of dermatological reactions, including toxic epidermal necrolysis and erythema multiforme, have been reported. The following adverse drug events may be borne in mind as potential effects of the components of this product. Potential effects of high dosage are listed in the OVERDOSAGE section. *Acetaminophen:* allergic reactions, rash, thrombocytopenia, agranulocytosis. *Caffeine:* cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

DRUG ABUSE AND DEPENDENCE: Abuse and Dependence: Butalbital: *Barbiturates may be habit-forming:* Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decreasing the daily dosage as tolerated by the patient.

OVERDOSAGE: Following an acute overdosage of Esgic-plus™ Tablets, toxicity may result from the barbiturate or the acetaminophen. Toxicity due to caffeine is less likely, due to the relatively small amounts in this formulation. **Signs and Symptoms:** Toxicity from barbiturate poisoning includes drowsiness, confusion, and coma; respiratory depression; hypotension; and hypovolemic shock. In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necroses, hypoglycemic coma and thrombocytopenia may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion. In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams. Acute caffeine poisoning may cause insomnia, restlessness, tremor, and delirium, tachycardia and extrasystoles. **Treatment:** A single or multiple overdose with this combination product is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended. Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Pressors should be avoided. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration. If renal function is normal, forced diuresis may aid in the elimination of the barbiturate. Alkalinization of the urine increases renal excretion of some barbiturates, especially phenobarbital. Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously. If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals. Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

Toxic Doses (for adults): Butalbital: toxic dose 1g (20 tablets); Acetaminophen: toxic dose 10g (20 tablets); Caffeine: toxic dose 1g (25 tablets). CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by: MIKART, INC., Atlanta, GA 30318
Distributed by: FOREST PHARMACEUTICALS, INC., Subsidiary of Forest Laboratories, Inc., St. Louis, MO 63045

Revised 3/94 Code 374A00

FOREST PHARMACEUTICALS, INC.
UAD LABORATORIES
St. Louis, Missouri 63045

ACULAR®
(ketorolac tromethamine) 0.5%
Sterile Ophthalmic Solution

INDICATIONS AND USAGE

ACULAR® ophthalmic solution is indicated for the relief of ocular itching due to seasonal allergic conjunctivitis.

CONTRAINDICATIONS

ACULAR® ophthalmic solution is contraindicated in patients while wearing soft contact lenses and in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

WARNINGS

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory agents. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With some nonsteroidal anti-inflammatory drugs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

PRECAUTIONS

General: It is recommended that ACULAR® ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: An 18-month study in mice at oral doses of ketorolac tromethamine equal to the parenteral MRHD (Maximum Recommended Human Dose) and a 24-month study in rats at oral doses 2.5 times the parenteral MRHD, showed no evidence of tumorigenicity. Ketorolac tromethamine was not mutagenic in Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac did not cause chromosome breakage in the *in vivo* mouse micronucleus assay. At 1590 ug/mL (approximately 1000 times the average human plasma levels) and at higher concentrations ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells. Impairment of fertility did not occurin male or female rats at oral doses of 9 mg/kg (53.1 mg/m^2) and 16 mg/kg (94.4 mg/m^2) respectively.

Pregnancy: Pregnancy Category C. Reproduction studies have been performed in rabbits, using daily oral doses at 3.6 mg/kg (42.35 mg/m^2) and in rats at 10 mg/kg (59 mg/m^2) during organogenesis. Results of these studies did not reveal evidence of teratogenicity to the fetus. Oral doses of ketorolac tromethamine at 1.5 mg/kg (8.8 mg/m^2), which was half of the human oral exposure, administered after gestation day 17 caused dystocia and higher pup mortality in rats. There are no adequate and well-controlled studies in pregnant women. Ketorolac tromethamine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Caution should be exercised when ACULAR® is administered to a nursing woman.

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

ADVERSE REACTIONS

In patients with allergic conjunctivitis, the most frequent adverse events reported with the use of ACULAR® ophthalmic solution have been transient stinging and burning on instillation. These events were reported by approximately 40% of patients treated with ACULAR® ophthalmic solution. In all development studies conducted, other adverse events reported during treatment with ACULAR® include ocular irritation (3%), allergic reactions (3%), superficial ocular infections (0.5%) and superficial keratitis (1%).

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REFERENCES: 1. Data on file, Fisons Corporation, 1985. 2. Data on file, Allergan, Inc., 1994. 3. IMS Data, December, 1994.

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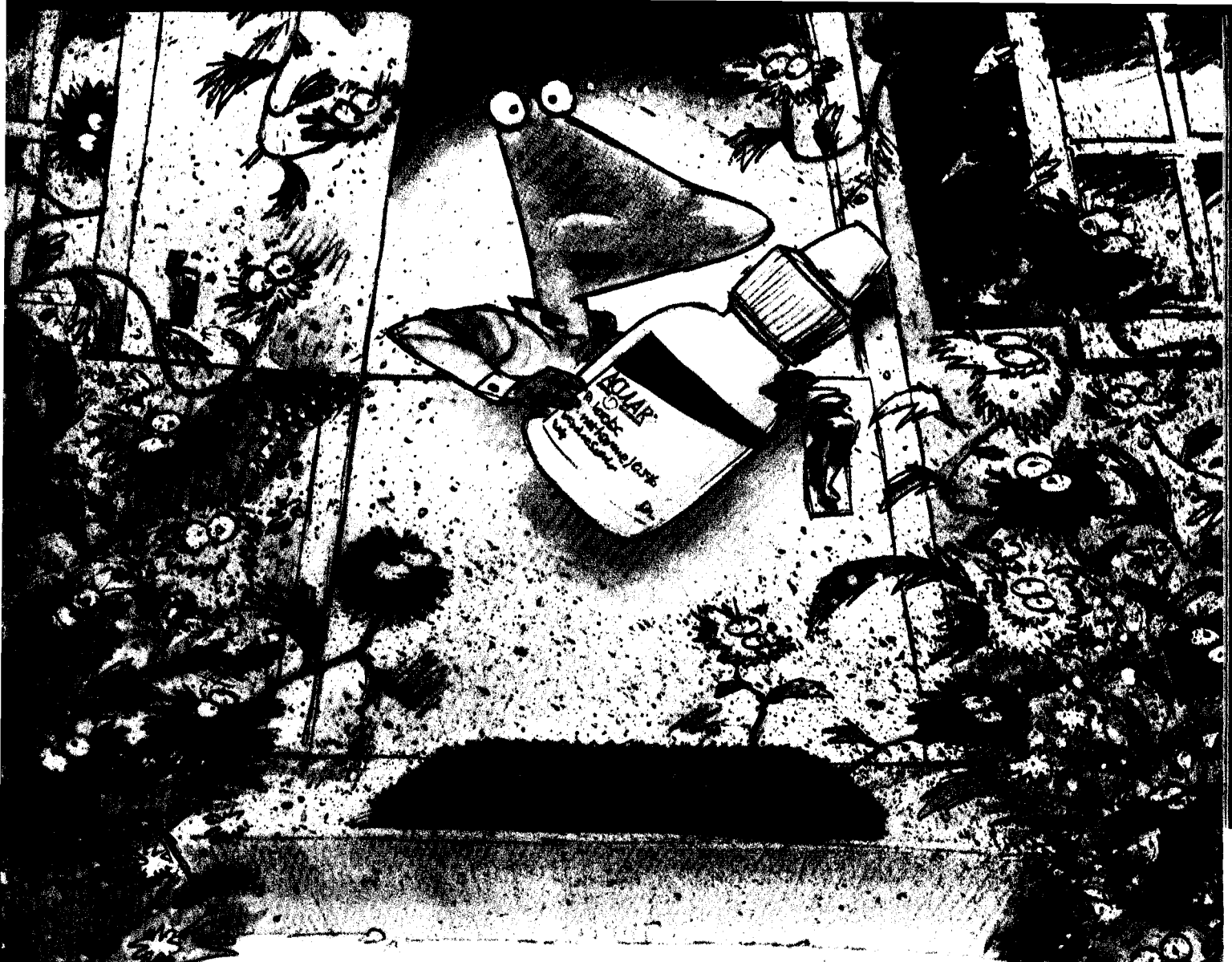

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In a recent survey (n=272), the vast majority of responding patients confirmed that ACULAR® stopped their ocular itching quickly and effectively.[2] Plus, ACULAR® has a favorable safety profile. There are no steroid-like side effects that can alter intraocular pressure, and no decongestant-like side effects, i.e., no risk to patients with narrow chamber angles.

So help rescue eyes from itching with ACULAR,® the #1 prescribed ophthalmic preparation[3] for the #1 patient complaint of seasonal allergic conjunctivitis — ocular itch. Because annoying antigens prey on more than just the nose.

The most frequently reported adverse events have been transient stinging and burning on instillation (approximately 40%). Not for use while wearing soft contact lenses.

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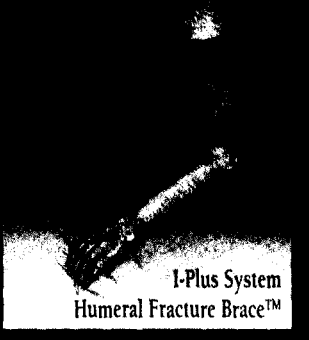

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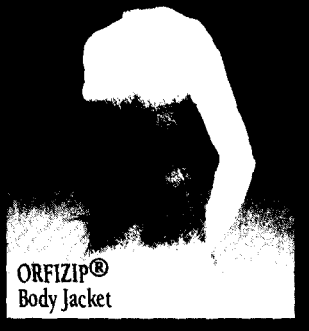

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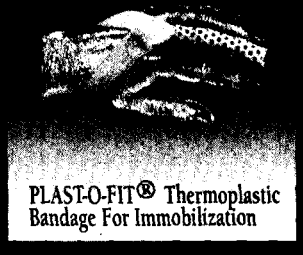

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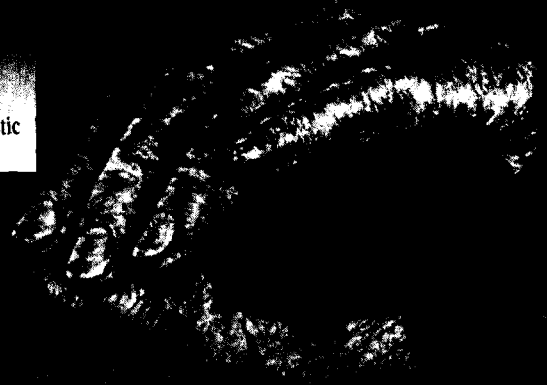

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Morrow JD, Margolies GR, Rowland J, Roberts LJ 2nd. Evidence that histamine is the causative toxin of scombroid-fish poisoning. N Engl J Med 1991; 324:716-20.

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Clinical Experience Network (CEN). A large-scale, office-based study evaluates the use of a new class of nonse dating antihistamines. A report from CEN. J Am Board Fam Pract 1990; 3:241-58.

Book

Rakel RE. Textbook of family practice. 4th ed. Philadelphia: WB Saunders, 1990.

Chapter in Book

Haynes RC Jr. Agents affecting calcification: calcium, parathyroid hormone, calcitonin, vitamin D, and other compounds. In: Gilman AG, Rall TW, Nies AS, Taylor P, editors. Goodman and Gilman's the pharmacological basis of therapeutics. 8th ed. New York: Pergamon Press, 1990.

Government Agency

Schwartz JL. Review and evaluation of smoking cessation methods: the United States and Canada, 1978-1985. Bethesda, MD: Department of Health and Human Services, 1987. (NIH publication no. 87-2940.)

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