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INDICATIONS AND USAGE

This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia

Elevated serum potassium levels (≥5.5 mEq/L). Discontinue if hyperkalemia develops Concomitant use with other potassium-sparing agents. Concomitant potassium supplementation. Anuria, acute and chronic renal insufficiency, significant renal impairment Hypersensitivity to either component or to other sulfonamide derived drugs

WARNINGS

Hyperkalemia: Abnormal elevation of serum potassium levels (25.5 mEq/L) can occur with all potassium conserving agents including MAXZIDI. Hyperkalemia is more likely to occur in patients with renal impairment, diabetes (even without evidence of renal impairment), or elderly or severely ill patients. Since uncorrected hyperkalemia may be fatal, serum potalevels must be monitored at frequent intervals, especially in patients first receiving MAXZIDE when dosages are changed, or with any illness that may influence renal function

Obtain ECG if signs and symptoms of hyperkalemia occur. Discontinue MAXZIDE immediately if hyperkalemia is present. If the serum potassium level exceeds 6.5 mEq/L more vigorous therapy is required. Avoid MAXZIDE in diabetic patients. If used, monitor scrum electrolytes. Avoid in severely ill patients in whom respiratory or metabolic acidesis may occur If MAXZIDE is used, frequently evaluate acid/base and serum electrolytes.

Use cautiously, if at all, with angiotensin-converting enzyme (ACE) inhibitors. (See PRECAUTIONS, Drug Interactions.)

Monitor for fluid or electrolyte imbalances at appropriate intervals. Do frequent serum and urine electrolyte determinations (especially when the patient is vomiting or receiving parenteral fluids). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy usually is water restriction. In actual salt depletion, appropriate replacement is the therapy of choice.

Hypokalemia may develop with thiazide therapy, especially with brisk diaresis, when severe cirrhosis is present, or during concomitant use of corticosteroids. ACTH, amphotericin It or after prolonged thiazide therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia

hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (eg. increased ventricular irritability).

MAXZIDE may produce an elevated blood urea nitrogen level (BUN), creatinine level, or both Elevations in BUN and creatinine levels may be more frequent in patients receiving divided dose

diuretic therapy. Discontinue if azotemia increases.

Use with caution in patients with impaired hepatic function or progressive liver disease and in patients with histories of renal lithiasis. Trianterene is a weak folic acid antagonist. Periodic blood evaluations are recommended. Hyperunicemia may occur or acute gont may be environmental in control of the progressive liver. ecipitated in certain patients receiving thiazide therapy. The thiazides may decrease serian

PBI level without signs of thyroid disturbance.

Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland with hypercalcentia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. Discontinue thiazides before conducting tests for parathyroid

Through requirements in diabetic patients may be changed. Thiazides may cause manifestation of latent diabetes mellitus. Sensitivity reactions to thiazides may occur in patients with or

MAXZIDE and MAXZIDE 25 MG Tablets Triamterene and Hydrochlorothiazide

without a history of allergy or bronchial asthma. Possible exactrbation or activation of systemic lupus crythematosus by thiazides has been reported

Thiazides may add to or potentiate the action of other anthypertensive drugs. Thiazides may decrease aftertal responsiveness to norepinephrine. Thiazides have also been shown to increase responsiveness to tubis oratine. Dioretics reduce renal clearance of lithium and increase the

risk or infinite lockety.

A one regal failure has been reported to a few patients receiving indomethacm and other formulations containing triantierene and hydrochlorothiazide. Caution is therefore advised when administering nonsteroidal anti-inflammatory agents with MAXIDI.

Use potassium-sparing agents vere cautionish if a all, in comparation with augustensin converting enzyme (ACI) inhibitors due to a greatly increased risk of hyperbalemia. Monitor

MAXZIDE may interfere with quinidine measurement. Pregnancy Category C: Thiazides cross the placental barner and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaunidice thromboxytopenia, panereatitis, and possibly other adverse reactions which have occurred in

Thiazides appear in breast milk If use is essential, the patient should stop nursing. Advanta-information on use in children is not available.

ADVERSE REACTIONS

Side effects observed in association with the use of MAXZIDE, other combination products containing trianiterene/hydrochlorothiazide, and products containing trianiterene hydrochlorothiazide include the following:

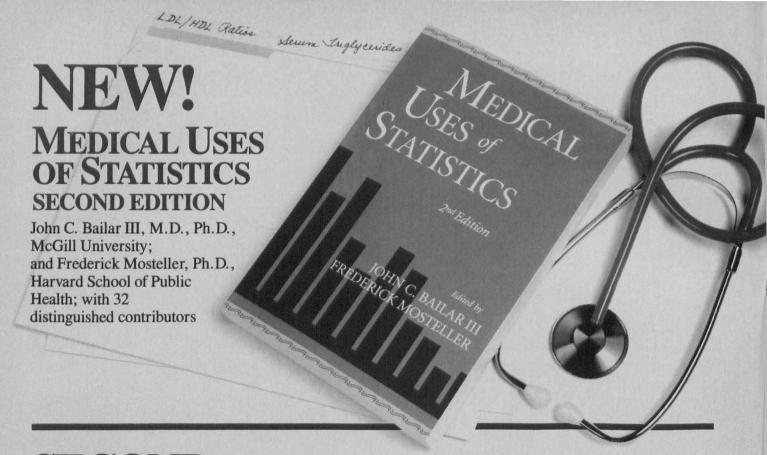
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Rev. 5/80 24025

- Schnaper HW. Maxwell MH. Efficacy and safety of trianterene/hydrochlorothiazide combinations in mild systemic hypertension. *Am.J. Cardiol.* 1989; 65-528-56B. Data on file, Lederle Laboratories, Pearl River, NY.
- Physicians' Desk Reference (PDR'), ed. 15. Oradell, M. Medical Economics Co.Inc. 1991



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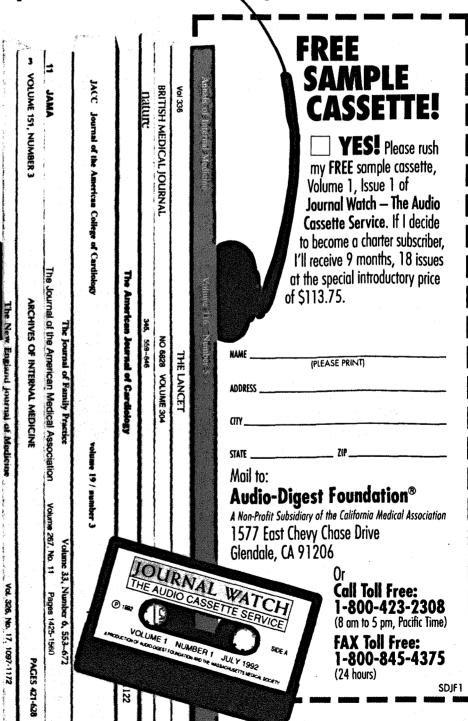
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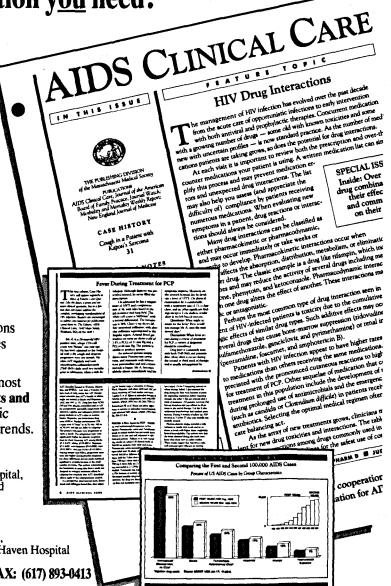


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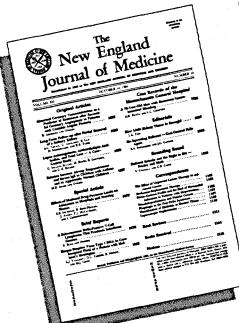
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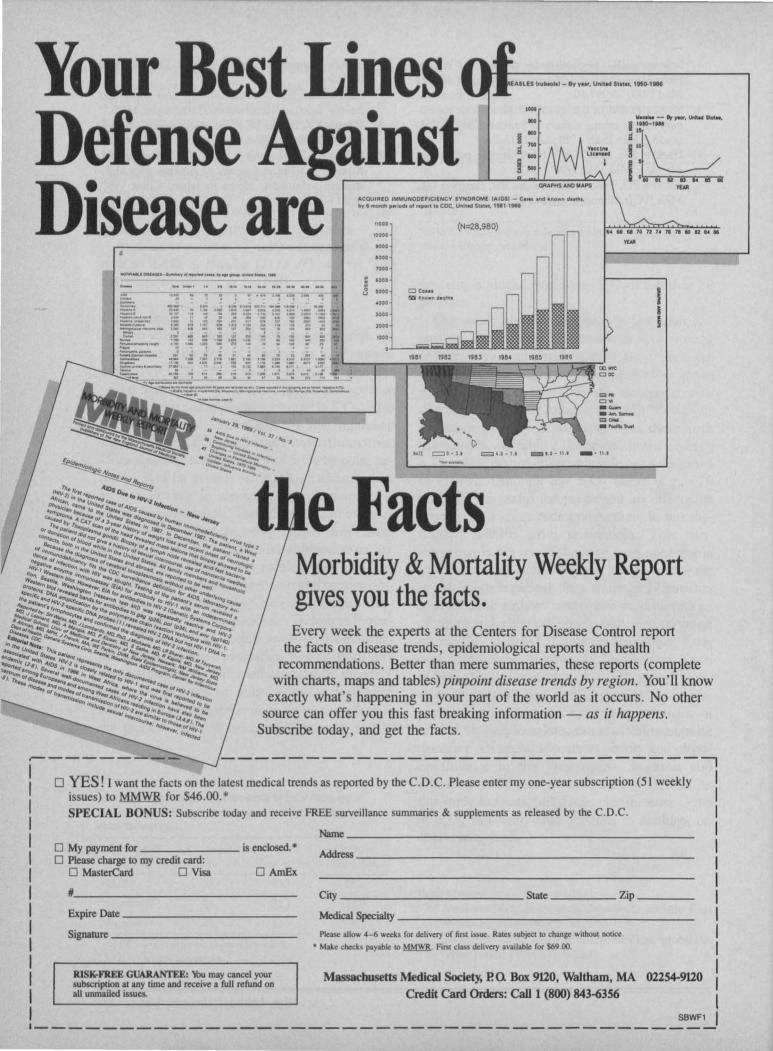
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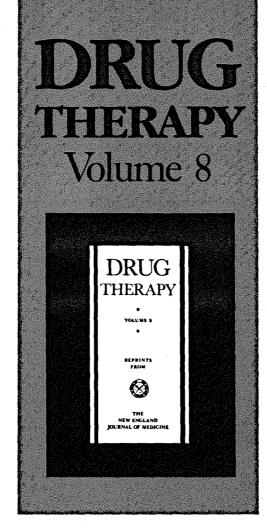
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Peripheral Vascular Disease: β-antagonists reduce cardiac output and can precipitate/aggravate arterial insufficiency in patients with peripheral or mesenteric vascular disease. Exercise caution and observe such patients closely for progression of arterial obstruction.

Bronchospastic Diseases: Patients with Bronchospastic Disease Should, in General, Not Receive a β -Blocker. Because of its relative β_1 -selectivity, low doses of SECTRAL may be used cautiously in such patients who do not respond to, or cannot tolerate, alternative treatment. Since β_1 -selectivity is not absolute and is dosedependent, use lowest possible dose of SECTRAL initially, preferably in divided doses. Make bronchodilator, e.g., theophylline, or a β_2 -stimulant, available in advance with instructions for use.

Instructions for use. Aneathesia and Major Surgery: The necessity/desirability of withdrawing β-blockers prior to major surgery is controversial; the heart's impaired ability to respond to β-adrenergically mediated reflex stimuli may enhance the risk of excessive myocardial depression during general anesthesia. Difficulty in restarting and maintaining the heartbeat also has been reported with beta-blockers. If treatment is continued, take special care when using anesthetics that depress the myocardium; use lowest possible SECTRAL dose. SECTRAL, like other β-blockers, is a competitive inhibitor of β-receptor agonists, so its effects can be reversed by cautious administration of such agents (e.g., dobutamine or isoproterenol). Symptoms of excessive vagal tone (e.g., profound bradycardia, hypotension) may be corrected with atropine.

arropine.

Diabetes and Hypoglycemia: β-blockers may potentiate insulin-induced hypoglycemia and mask some symptoms such as tachycardia; dizziness and sweating are usually not significantly affected. Warn diabetics of possible masked

Thyrotoxicosis: β-adrenergic blockade may mask some clinical signs (tachycardia) of hyperthyroidism. Abrupt withdrawal of SECTRAL may precipitate a thyroid storm in patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal or Hepatic Function: While there are no U.S.

PRECAUTIONS: Impaired Renal or Hepatic Function: While there are no U.S. studies, foreign published experience shows that acebutolol has been used successfully in chronic renal insufficiency. Acebutolol is excreted via the G.I. tract, but the active metabolite, diacetolol, is eliminated mainly by the kidney. A linear relationship exists between renal clearance of diacetolol and creatinine clearance (Cl_{Cl}); reduce daily dose of acebutolol by 50% when Cl_{Cl} is less than 50 mL/min and by 75% when it is less than 25 mL/min. Use cautiously in patients with impaired hepatic function.

SECTRAL has been used successfully and without problems in elderly patients in U.S. clinical trials without specific dosage adjustment. However, in the elderly, lower maintenance doses may be required because bioavailability of SECTRAL and its

metabolite are approximately doubled.

Information for Patients: Warn patients, especially those with evidence of coronary artery disease, against interruption or discontinuation of SECTRAL without physician supervision. Although cardiac failure rarely occurs in properly selected patients, advise patients to consult a physician if signs or symptoms suggestive of impending OHE or unexplained respirators, symptoms develop.

CHF, or unexplained respiratory symptoms, develop.

Warn patients of possible severe hypertensive reactions from concomitant use of α-adrenergic stimulants, e.g., nasal decongestants used in OTC cold medicines and easal drops.

Citalical Laboratory Findings: SECTRAL, like other β-blockers has been associated with development of antinuclear antibodies (ANA). In prospective clinical trials, patients receiving SECTRAL had a dose-dependent increase in the development of positive ANA titers. Symptoms related to this laboratory abnormality were intequent. Symptoms and ANA titers were reversible upon discontinuation of SECTRAL.

Drug Interactions: Catecholamine-depleting drugs may have additive effects when given with β-blockers. Observe patients treated with both agents closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/ presyncope, or orthostatic changes in blood pressure without compensatory tachycardia. Exaggerated hypertensive responses have been reported from use of β-adrenergic antagonists with α-adrenergic stimulants, including those in OTC cold remedies and vasoconstrictive nasal drops. Nonsteroidal anti-inflammatory drugs may blunt antihypertensive effects of beta-blockers.

blunt antihypertensive effects of beta-blockers.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies in rats and mice, at doses 15 times the maximum recommended (60 kg) human dose, did not indicate carcinogenic potential for SECTRAL. Diacetolol, the major metabolite in man, was without carcinogenic potential in rats at doses up to 1800 mg/kg/d. SECTRAL and diacetolol also had no mutagenic potential in the Ames Test. No significant impact on reproductive performance or fertility was found in rats tollowing SECTRAL or diacetolol doses of up to 240 or 1000 mg/kg/d, respectively.

Pregnancy: Teratogenic Effects: Pregnancy Category B: No teratogenic effects were seen in rat or rabbit reproduction studies utilizing SECTRAL doses that were, respectively, approximately 31.5 and 6.8 times the maximum recommended human dose. At this dose in the rabbit, slight fetal growth retardation was noted; this was considered to be a result of maternal toxicity (evidenced by reduced food intake, lowered rate of body weight gain, mortality). Diacetolol studies (doses up to 450 mg/kg/d in rabbits and up to 1800 mg/kg/d in rats) showed no evidence of fetal harm other than a significant elevation in postimplantation loss with 450 mg/kg/d, a level at which food consumption and body weight gain were reduced in rabbit dams; there was a nonstatistically significant increase in incidence of bilateral cataract in rat fetuses from dams treated with 1800 mg/kg/d. There are no adequate and well-controlled trials in pregnant women; SECTRAL should be used during pregnancy only if potential benefit justifies risk to the fetus.

If potential benefit justifies risk to the fetus.

Nonteratogenic Effects: Human studies indicate that acebutolol and diacetolol cross the placenta. Neonates of mothers who received acebutolol during pregnancy have reduced birth weight, decreased blood pressure, and decreased heart rate.

Labor and Delivery: Effect on labor and delivery in pregnant women is unknown.

Animal studies have shown no effect of SECTRAL on the usual course of labor and delivery.

Nursing Mothers: Acebutolol and diacetolol appear in breast milk (milk: plasma ratio of 7.1 and 12.2, respectively). Use in nursing mothers is not recommended.

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

ADVERSE REACTIONS: SECTRAL is well tolerated in properly selected patients.

Most adverse effects have been mild, not required therapy discontinuation, and tended to decrease as treatment duration increases.

The incidence of treatment-related side effects (volunteered and elicited) derived

The incidence of treatment-related side effects (volunteered and elicited) derived from U.S. controlled clinical trials in patients with hypertension, angina and arrhythmia follows. Numbers represent percentage incidence for SECTRAL (N =1002) versus placebo (N=314), respectively.

placebo (N=314), respectively.

Cardiovascular: Chest pain 2%, 1%; Edema 2%, 1%. CNS: Depression 2%,1%;

Dizziness 6%, 2%; Fatigue 11%, 4%; Headache 6%, 4%; Insomnia 3%, 1%; Abnormal dreams 2%, 1%. Dermatologic: Rash 2%, 1%. Gastrointestinal: Constipation 4%, 0%; Diarrhea 4%, 1%; Dyspepsia 4%, 1%; Flatulence 3%, 1%; Nausea 4%, 0%.

Genitourinary: Micturition (frequency) 3%, <1%. Musculoskeletal: Arthralgia 2%, 2%; Myalgia 2%, 0%. Respiratory: Cough 1%, 0%; Dyspnea 4%, 2%; Rhinitis 2%, <1%.

Special Senses: Abnormal Vision 2%, 0%.

The following selected (potentially important) side effects were seen in up to 2% of SECTRAL patients: Cardiovascular: hypotension, bradycardia, heart failure. CNS: anxiety hyper/hypoesthesia, impotence. Skin: pruritus. Gastrointestinal: vomitting, abdominal pain. Genitourinary: dysuria, nocturia. Liver and Biliary: small number of reported cases of liver abnormalities (increased SGOT, SGPT, LDH). In some cases, increased bilirubin or alkaline phosphatase, fever, malaise, dark urine, anorexia, nausea, headache, and/or other symptoms have been reported. In some cases, symptoms and signs were confirmed by rechallenge. Abnormalities were reversible upon drug cessation. Musculoskeletal: back and joint pain. Respiratory: pharyngitis, wheezing. Special Senses: conjunctivitis, dry eye, eye pain. Autoimmune: extremely rare reports of systemic lupus erythematosis.

Incidence of drug-related adverse effects (volunteered and solicited) based on SECTRAL dose is shown below. (Data from 266 hypertensive patients treated for 3 months on a constant dose.)

Body System	400 mg/day (N = 132)	800 mg/day (N = 63)	1200 mg/day (N = 71)
Cardiovascular	5%	2%	1%
Gastrointestinal	3%	3%	7%
Musculoskeletal	2%	3%	4%
Central Nervous System	9%	13%	17%
Respiratory	1%	5%	6%
Skin	1%	2%	1%
Special Senses	2%	2%	6%
Genitourinary	2%	3%	1%

Potential Adverse Effects: Certain adverse effects not listed above have been reported with other β -blocking agents and should be considered as potential adverse effects of SECTRAL.

CNS: Reversible mental depression progressing to catatonia, an acute syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS). Allergic: Erythematous rash, lever with aching and sore throat, laryngospasm, respiratory distress.

Hematologic: Agranulocytosis, nonthrombocytopenic and thrombocytopenic purpura. Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis. Miscellaneous: Reversible alopecia, Peyronic's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with SECTRAL.

Keep at room temperature, Approximately 25°C (77°F).

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