medi-notes

THOMAS WESLEY ALLEN, D.O. Editor in Chief

Obesity and the autonomic nervous system

Body fat percentages and sympathetic and parasympathetic activity are inversely correlated, suggesting involvement of more than one organ system.

In a study of 56 healthy men with varying degrees of body fat, the autonomic indexes in the cardiovascular system, eye, and adrenal medulla decreased as body fat percentage increased. Several organ systems were studied simultaneously using pupillometry, variation in R-R intervals, and other assessments.

Further studies that examine the autonomic nervous system in obese persons should be performed to determine its role in subgroups of patients, such as those overweight hypertensives and persons having difficulty losing or maintaining weight loss due to autonomic nervous system malfunction.

Peterson HR, Rothschild M, Weinberg CR, et al: Body fat and the activity of the autonomic nervous system. N Engl J Med 1988;318:1077-1083.

Indomethacin effects on the fetal ductus arteriosus

Transient constriction of the ductus arteriosus occurs in some fetuses after indomethacin administration. Thirteen pregnant women experiencing premature labor were given indomethacin in three different dose schedules from 100 mg to 175 mg daily for up to three days. Echocardiography found 50% of fetuses had ductal constriction. Three of these seven instances were associated with tricuspid regurgitation.

This study suggests that patent ductus arteriosus in a fetus after 24 to 36 hours of indomethacin therapy indicates that the drug's constrictive effects on the duct have been avoided. However, weekly echocardiography may be necessary during long-term therapy.

Moise KJ, Huhta JC, Sharif DS, et al: Indomethacin in the treatment of premature labor: Effects on the fetal ductus arteriosus. *N Engl J Med* 1988;319:327-331.

Early onset hepatic disease and mental, physical development in children

Youngsters whose chronic liver disease began within the first year of life scored significantly lower on IQ tests, including verbal and performance skills, than children in whom hepatic disease occurred between 17 months to 12 years of age. Thirty-six children took part in this study; 21 comprised the former group while 15 made up the latter.

Delays in intellectual development were found most frequently in patients with prolonged liver disease. This group also exhibited smaller head and mean arm circumference and stature; vitamin E deficiency; and reduced -glutamyl transpeptidase levels than those children with no mental deficits.

Based on these findings, the authors suggest aggressive nutritional management, such as elemental formula or nasogastric feeding, for optimal growth and development in children whose liver disease manifests itself during early life. Liver transplantation in children even younger than 1 year is advocated because of the effect of hepatic dysfunction on intellectual development.

Stewart SM, Uauy R, Kennard BD, et al: Mental development and growth in children with chronic liver disease of early and late onset. *Pediatrics* 1988;82:167-172.

Rapid eye test detects drug abuse

Because of its low cost and relative ease of application, the rapid eye test can be used by nurses and, after training, law enforcement personnel to detect suspected drug abuse.

Each drug class manifests itself in pupil size and reaction, nystagmus, convergence, and corneal reflex. Positive results from the rapid eye test should be confirmed by traditional blood and urine samples.

Tennant F: The rapid eye test to detect drug abuse. Postgrad Med 1988;84:108-114.

Brain herniation and diabetic ketoacidosis

The more rapid the rate of rehydration, the quicker the onset of brain herniation. This conclusion was reached after a retrospective review of 42 cases involving brain herniation during treatment for severe diabetic ketoacidosis.

While the previous limit of 4 L/m² of fluid administration per day remains the standard for rehydration, 10% of the patients studied here received less than this suggested amount. Although this implies other factors are responsible, until the etiology is better understood, the authors suggest this fluid administration guideline be followed for the first day's therapy, especially when the patients shows normal renal and cardiac function. However, the coexistence of shock or abnormally low central venous pressure indicates a temporary need for more rapid fluid administration.

Duck SC, Wyatt DT: Factors associated with brain herniation in the treatment of diabetic ketoacidosis. *J Pediatrics* 1988;113:10-13.

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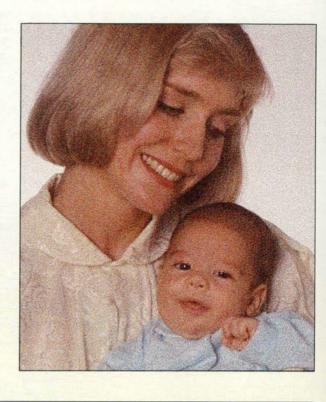
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May prevent allergic manifestations in infants with a family history of allergy²

Routine Feeding of Normal Infants Nutritionally complete for optimal growth and development

References:

- Committee on Nutrition, American Academy of Pediatrics: Pediatric Nutrition Handbook, ed 2, Forbes GB, Woodruff CW (eds). Elk Grove Village, Ill, American Academy of Pediatrics, 1985, p 210.
- 2. Vandenplas Y, Deneyer M, Sacre L, et al: Preliminary data on a field study with a new hypo-allergic formula. *Eur J Pediatr*, to be published.
- 3. Kahn A, Rebuffat E, Blum D, et al: Difficulty in initiating and maintaining sleep associated with cow's milk allergy in infants. Sleep 1987;10:116-121.
- 4. Zabransky S, Zabransky M: Preliminary clinical experience with a hypoaller-genic infant formula. Extracta Paediatrica 1987;11:10-22.
- 5. Schmidt E, Reinhardt D, Gerke R: The use of hypoallergenic milk formulas in newborns. *Der Kinderarz*t 1987;5:627-631.
- 6. Denis R, Willeme D: Data on file, Carnation Co.



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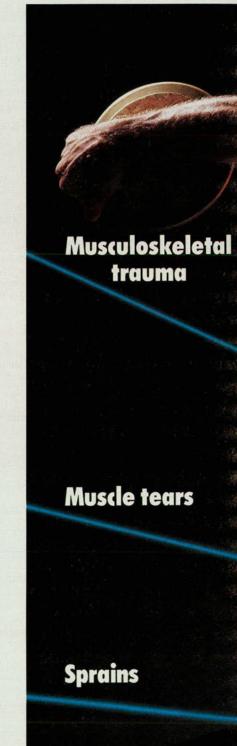
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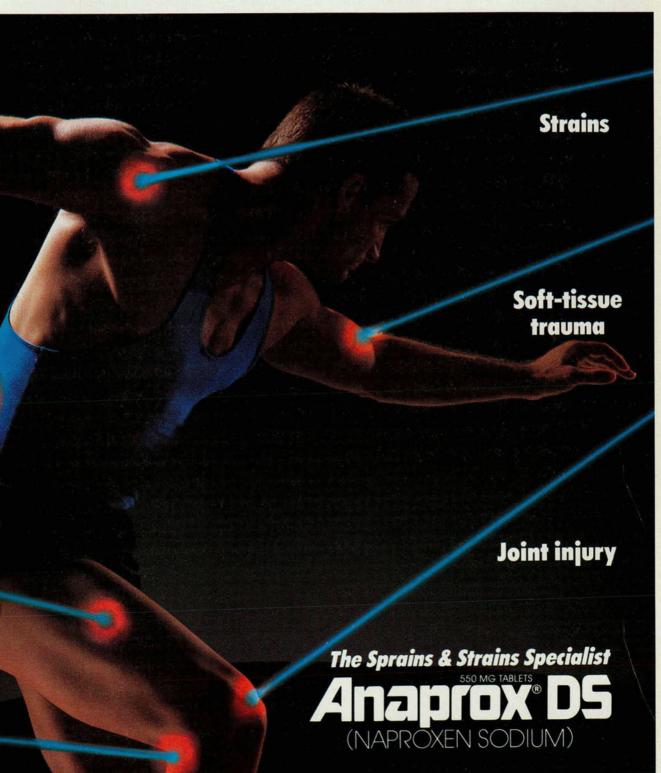
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Contraindications: Patients who have had allergic reactions to NAPROSYN.

ANAPROX or AMAPROX DS or in whom aspirin or other NSAIDs induce the syndrome of asthma, thinitis, and nasal polyps. Because anaphylactic reactions

usually oper in patients with a believe of the contraints. usually occur in patients with a history of such reactions, question patients for asthma, nasal polyps, urticaria, and hypotension associated with NSAIDs

astime, lasar polyps, a dealts, and impotension associated with institute before starting therapy. If such symptoms occur, discontinue the drug, Warnings: Peptic ulcers and GI bleeding have been reported in patients on NSAIDs, including naprosen sodium. In patients with GI bleeding or active peptic ulcer, start an anti-ulcer regimen, weigh benefits and risks of treatment, and monitor patient. Give to patients with history of GI disease only under close

supervision and after reading Adverse Reactions section.

Precautions: DO NOT GIVE NAPROSYN® (NAPROXEN) CONCOMITANTLY WITH ANAPROX® OR ANAPROX® DS (NAPROXEN SODIUM) SINCE BOTH CIRCULATE IN PLASMA AS THE NAPROXEN ANION. Acute interstitial nephritis with hematu ria, proteinuria, and nephrotic syndrome has been reported. Patients with impaired renal function, heart failure, liver dysfunction, taking diuretics, and the elderly are at greater risk of overt renal decompensation. If this occurs, dis-continue the drug. Use with caution and monitor serum creatinine and/or creatinine clearance in patients with significantly impaired renal function. Use caution in patients with baseline creatinine clearance less than 20 ml/minute. Use the lowest effective dose in the elderly or in patients with chronic alcoholic Use the lowest effective dose in the energy of in planeins with Chronical liver disease or cirrhosis. With NSAIDs, borderline elevations of liver tests may occur in up to 15% of patients. They may progress, remain unchanged, or be transient with continued therapy. Elevations of SGPT or SGOT occurred in con-trolled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and fatal hepatitis, have been reported rarely. If liver disease develops or if systemic manifestations occur (e.g., eosinophilia or rash), discon develops or if systemic manifestations occur (e.g., eosinophilia or rash), discon-tinue therapy, if steroid dosage is reduced or eliminated during therapy, do so slowly and observe patients closely for adverse effects, including adrenal insuf-ficiency and exacerbation of arthritis symptoms. Determine hemoglobin values periodically for patients with initial values of 10 grams or less who receive long-term therapy, Peripheral edema has been reported. For patients with restricted sodium intake, note that each tablet contains approximately 25 mg or 50 mg (1 or 2 mEq) sodium. Use with caution in patients with fluid retention, hyper-tenient or best follow. The dorse active residence of the formation active. tension or heart failure. The drug's antipyretic and anti-inflammatory activities may reduce fever and inflammation, diminishing their diagnostic value. Conduct ophthalmic studies if any change or disturbance in vision occurs.

Information for Patients: Patients should use caution for activities requir

ing alertness if they experience drowsiness, dizziness, vertigo or depression Drug Interactions: Use caution when giving concomitantly with coumarin type anticoagulants; a hydantoin, sulfonamide or sulfonylurea; furosemide; lith ium; beta-blockers; probenecid; or methotrexate.

Drug/Laboratory Test Interactions: The drug may decrease platelet aggrega tion and prolong bleeding time or increase urinary values for 17-ketogenic ste

tion and prioring because the many and the second throughout the condition and the c

Avoid use during late pregnancy.

Nursing Mothers: Avoid use in nursing mothers.

Pediatric Use: Single doses of 2.5-5 mg/kg (as naproxen suspension), with total daily dose not exceeding 15 mg/kg/day, are safe in children over

Adverse Reactions: In a study, GI reactions were more frequent and severe in rheumatoid arthritis patients on 1650 mg/day naproxen sodium than in those on 825 mg/day. In studies in children with juvenile arthritis, rash and prolonged bleeding times were more frequent, GI and CNS reactions about the same, and bleeding times were more frequent, GI and CNS reactions about the same, and other reactions less frequent than in adults Incidence Greater Than 19, Probable Causal Relationship. GI. The most frequent complaints related to the GI tract: constipation, heartburn, abdominal pain, nausea, dyspepsia, diarrhea, stomatitis CNS. headache, disciness, flowshiess, light-headeness, vertigo. Dermatologic: itching (pruritus), skin eruptions, ecchymoses, sweating, purpura Special Senses: tinnitus, hearing disturbances, visual disturbances. Cardiovascular: edema, dyspinar, apolitications. General: thirst: "Incidence of reported reaction 3%-9%. Where unmarked, incidence less than 3%. Incidence Less Than 1%: Probable Causal Relationship: GI. abnormal liver function tests colitis. GI bleeding and/or perforation hematemesis; isuandice, melena. tests, colitis, Gi bleeding and/or perforation, hematemesis, jaundice, melena, peptic ulceration with bleeding and/or perforation, womiting. Renal: glomerular nephritis, hematurai, interstitial nephritis, nephrotic syndrome, renal disease. Hematologic: agranulocytosis, eosinophilia, granulocytopenia, leukopenia, thrombocytopenia. CNS: depression, dream abnormalities, inability to concentrate, insomnia, malaise, myalgia and muscle weakness. Dermatologic: alope cia, photosensitive dermatitis, skin rashes. Special Senses: hearing impairment. Cardiovascular: congestive heart failure. Respiratory: eosinophilic pneumonitis. General: anaphylactoid reactions, menstrual disorders, pyrexia chills and fever). Causal Relationship Unknown: Hematologic: aplastic anemia hemolytic anemia. CNS: cognitive dysfunction. Dermatologic: epidermal necrol ysis, erythema multiforme, Stevens-Johnson syndrome, urticaria. Gl: non peptic gastrointestinal ulceration, ulcerative stomatitis. Cardiovascular: vasculitis. General: angioneurotic edema, hyperglycemia, hypoglycemia. Overdosage: May have drowsiness, heartburn, indigestion, nausea, von

Empty stomach and use usual supportive measures. In animals 0.5g/kg of activated charcoal reduced plasma levels of naproxen.

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Acute Tendinitis and Bursitis: The recommended starting dose is 550 mg, fol lowed by 275 mg every 6 to 8 hours, as required. The total daily dose should not

exceed 1375 mg.

Dosage and Administration for Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis: The recommended dose in adults is 275 mg or 550 mg twice daily. In patients who tolerate lower doses well, the dose may be increased to 1650 mg per day for limited periods when a higher level of anti-inflammatory/ analgesic activity is required. Observe sufficient increased clinical benefits to

offset potential increased risk.

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Balloon aortic valvuloplasty in elderly patients

Balloon aortic valvuloplasty is appropriate therapy for some elderly patients with symptomatic aortic stenosis. During a 2 1/2 year study involving 170 patients who had undergone this procedure, 168 patients experienced a significant increase in the mean aortic-valve area and cardiac output. Conversely, the peak aortic-valve pressure gradient significantly decreased.

Follow up averaged 9.1 months during which 25 patients died approximately 6.4 months after discharge. These deaths were in addition to the six that occurred in the hospital. Survival probability was 74% 12 months after the procedure.

Although symptoms recurred in 44 patients and restenosis remained common, the authors conclude that repeat balloon dilation serves as an appropriate management.

Safian RD, Berman AD, Diver DJ, et al: Balloon aortic valvuloplasty in 170 consecutive patients. N Engl J Med 1988;319:125-130.

Factors contributing to survival in dialysis patients

Age, renal diagnosis, dialysis type, and the year dialysis began are important predictors in survival of such patients. These factors became apparent during survival and risk analyses performed on 532 patients undergoing long-term dialysis beginning from 1970 to 1985.

Specifically, older patients with diabetes mellitus comprised the highest risk group. The starting dates were grouped into four-year periods. Those beginning dialysis before or after 1978 through 1981 experienced a 1.5 higher risk than those whose therapy began during that period. Home hemodialysis, which was most often chosen by younger patients with lower incidences of diabetes mellitus and renal vascular disease, decreased risk fivefold when compared with other dialysis modalities.

While high risk patients have an

increased mortality, overall survival has improved.

Mailloux LU, Bellucci AG, Mossey RI, et al: Predictors of survival in patients undergoing dialysis. Am J Med 1988;84:855-862.

Endotoxemia and early detection of septicemia in febrile patients

Endotoxemia is a valid clinical indicator of gram-negative septicemia in febrile patients. The absence of endotoxemia has a negative predictive value of 99% when ruling out the risk of septicemia.

These findings resulted from a comparison of endotoxemia and bacteremia as indications of ensuing septicemia in 473 consecutive febrile patients. With the endotoxin assay, sensitivity, specificity, and the likelihood ratio for positive results were 79%, 96%, and 20, respectively. Bacteremia corresponding indices were 89%, 78%, and 4.

Van Deventer SJ, Buller HR, Ten Cate JW, et al: Endotoxemia: An early predictor of septicemia in febrile patients. Lancet 1988;1:605-608.

Loss of HIV-1 antibodies with evidence of viral infection in asymptomatic homosexual men

During a 2 1/2 year period, four asymptomatic homosexual men, initially found to be seropositive for human immunodeficiency virus type 1 (HIV-1), were found to be seronegative by the enzyme-linked immunosorbent assay and Western blot.

Six to 12 months after being positive, the Western blot for three patients did not detect any antibody bands; on the fourth, there was gradual fading in the number and intensity of bands. No HIV-1-p24 antigenemia was detected and cryopreserved peripheral blood mononuclear cells were negative for HIV-1. Other clinical and laboratory findings from these four patients were similar to seronegative persons.

The authors conclude while asymptomatic persons seropositive for HIV- In hypertension...



Tenoretic®

Each tablet contains:

TENORMIN* (atenoiol) 50 mg or 100 mg and chlorthalidone 25 mg

Added control and convenience... without added side effects in a majority of patients... regardless of age, race, sex, and prior therapy.

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ONE TABLET A DAY enoretic

Please consult complete product information before prescribing. A summary follows:

TENORETIC (atenolol and chlorthalidone) is for the treatment of hypertension. It combines the antihypertensive activity of two agents: a beta₁-selective (cardioselective) hydrophilic blocking agent (atenolol, TENORMIN*) and a monosulfonamyl diuretic (chlorthalidone) Inactive ingredients: magnesium stearate, microcrystalline cellulose, povidone, sodium starch

in Indications and usage: TENORETIC is indicated for the treatment of hypertension. This fixed-dose combination drug is not indicated for initial therapy of hypertension. If the fixed-dose combination represents the dose appropriate to the individual patient's needs, it may be more

combination represents the dose appropriate to the individual patients needs, it may be more convenient than the separate components.

CONTRAINDICATIONS: TENORETIC is contraindicated in patients with: sinus bradycardia, heart block greater than first degree, cardiogenic shock, overt cardiac failure (see WARNINGS), anuria, hypersensitivity to this product or to sulfonamide-derived drugs.

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics. TENORETIC should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with

administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Fallure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients receiving TENORETIC should be digitalized and/or be given additional diuretic therapy. Observe the patient closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, TENORETIC therapy should be withdrawn.

Renal and Hepatic Disease and Electrolyte Disturbances: Since atenolol is excreted via the kidneys. TENORETIC should be used with caution in patients with impaired renal function. In patients with renal disease, thiazides may precipitate azotemia. Since cumulative effects may develop in the presence of impaired renal function, if progressive renal impairment becomes evident, TENORETIC should be discontinued.

In patients with impaired hepatic function or progressive liver disease, minor alterations in fluid and electrolyte balance may precipitate hepatic coma. TENORETIC should be used with caution in these patients.

patients.

Ischemic Heart Disease: Although not yet reported with atenoiol following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORETIC is planned, the patient should be activated to limit physical activity to a minimum. TENORETIC should be reinstated if withdrawal symptoms occur.

TENORETIC should be reinstated if withdrawal symptoms occur.

TENORETIC should be reinstated if withdrawal symptoms occur

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN

GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁-selectivity, however,

TENORETIC may be used with caution in patients with bronchospastic disease who do not

respond to, or cannot tolerate, other antihypertensive treatment. Since beta₇-selectivity is not

absolute, the lowest possible dose of TENORETIC should be used and a beta₇-striunulating

agent (bronchodilator) should be made available. If dosage must be increased, dividing the

dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs, it may be decided to

withdraw TENORETIC before surgery. In this case, 48 hours should be allowed to elapse between the

last dose and anesthesia. It treatment is continued, care should be taken when using anesthetic

agents because of the risk of further depression of the myocardium.

Beta blockers are competitive inhibitors of beta-receptor agonists and their effects on the heart can

be reversed by administration of such agents; eg, dobutamine or isoproterenol with caution (see

section on OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia,

hypotension) may be corrected with atropine (1-2 mg IV).

Metabolic and Endocrine Effects: TENORETIC may be used with caution in diabetic patients.

Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as

dizziness and sweating may not be significantly affected. Atenolol does not potentiate insulin-induced

hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to

normal levels.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent

diabetes mellitus may be evene manifest during abbeta blockers.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged, latent diabetes mellitus may become manifest during chlorthalidone administration. Beta-adrenergic blockade may mask certain clinical signs (ep. Lachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected developing thyrotoxicosis and from whom TENORETIC therapy is to be withdrawn should be monitored closely.

monitored closely.

Because calcium excretion is decreased by thiazides, TENORETIC should be discontinued before carrying out tests for parathyroid function. Pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy, however, the common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen.

Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide

PRECAUTIONS, General—Electrolyte and Fluid Balance Status: Periodic determination of serum

PRECAUTIONS, General—Electrolyte and Fluid Balance Status: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. Patients should be observed for clinical signs of fluid or electrolyte imbalance; ie, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and unne electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of the mouth, thirst, weakness, letnargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. 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). Hypokalemia may be avoided or treated by use of potassium supplements or loods with a high potassium content.

Any chloride delicit during thiazide therapy is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather, appropriate therapy is water restriction rather than administration of salt except in rare instances when the hyponatremia is life-threatening in actual salt depletion, appropriate replacement is the therapy of choice.

Drug Interactions: TENORETIC plus a catecholamine depletor (eg. reserpine) should be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not suf

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such preparations with TENORETIC.

Should it be decided to discontinue therapy in patients receiving TENORETIC and clonidine concurrently, the TENORETIC should be discontinued several days before the gradual withdrawal

Other Precautions: In patients receiving thiazides, sensitivity reactions may occur with or withor history of allergy or bronchial asthma. The possible exacerbation or activation of systemic lupus erythematosus has been reported. The antihypertensive effects of thiazides may be enhanced in

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing dura of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study with atenolol, each employing dose levels as high as 300 mg/kg/day or 150 times the maxim recommended human dose, did not indicate a carcinogenic potential in rodents. Atenolol was negative in the mouse dominant lethal test, the Chinese hamster in vivo cytogenetitest and the Salmonella typhimurium back mutation test (Ames test), with or without metabolic

test and the Salmonella typnimunum back mutation test (Ames test), with or without metabolic activation.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times to maximum recommended human dose) was unaffected by atenolol administration.

Use in Pregnancy: Pregnancy Category C. TENORETIC (atenolol and chlorthalidone) was stud for teratogenic potential in the rat and rabbit. Doses of 10, 100 and 300 mg/kg/day were administerably to pregnant rats, with no teratologic effects observed. Two studies were conducted in rabbits the first study, pregnant rabbits were dosed with 10, 100 or 200 mg/kg/day. No teratologic changes were noted: embryonic resorptions were observed at all dose levels (ranging from approximately 5 times to 100 times the maximum recommended human dose). In a second rabbit study, dosages w 5, 10 and 25 mg/kg/day. No teratogenic or embryotoxic effects were demonstrated. It is concluded that the no-effect level for embryonic resorptions is 25 mg/kg/day (approximately 12 5 times the maximum recommended human dose) or greater. TENORETIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Atenoloj.—Atenolol has been shown to produce a dose-related increase in embryo/fetal resorpti in rats at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There an oadequate and well-controlled studies in pregnant women.

Chlorthalidone and related drugs in pregnant women requires that the anticipated benefits of the de weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundic thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

rombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since ost drugs are excreted in human milk, nursing should not be undertaken by mothers receiving

TENORETIC

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

ADVERSE REACTIONS: TENORETIC is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient. The adverse effects observed for TENORETIC are essentially the same as those seen with the individual components.

Atenolol: The frequency estimates that follow derive from controlled studies in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg. by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both atenolol and place treated patients than when these reactions were volunteered. Where frequency of adverse effects atenolol and placebo is similar, causal relationship to atenolol is uncertain.

The data present these estimates in terms of percentages: first from the US studies (volunteered side effects) and then from both US and foreign studies (volunteered and elicited side effects): US STUDIES (% ATENOLOL-% PLACEBO):

side effects) and then from both US and foreign studies (volunteered and elicited side enecis): US STUDIES (% ATENOLO1-% PLACEED):
CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), ligh headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)
GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%)
RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS US AND FOREIGN STUDIES:

OVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension leg pain (3%-1%)

(4%-5%), leg pain (3%-1%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), ligheadedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)
GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)
RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)
MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the sympto have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if a such reaction is not otherwise explicable. Patients should be closely monitored following cessation therapy.

therapy.

Chlorthalidone: Cardiovascular: orthostatic hypotension; Gastrointestinal: anorexia. gastric irritati vomiting, cramping, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; CNS: veriigo, paresthesias, xanthospisa. Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia: Hypersensitivity: purpura, photosensitivity; rash, urticaria, necrotizing angilitis (vasculitis, cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis); Miscellaneous: hyperglycemia, glycosunia, hyperuricemia, muscles spasm, weakness, restlessness. Clinical trials in TENORETIC conducted in the United States (89 patients treated with TENORETIC) revealed no neupropreted advances effects.

unexpected adverse effects.

Potential Adverse Effects: In addition, a variety of adverse effects not observed in clinical trials with atenolol but reported with other beta-adrenergic blocking agents, should be considered poter adverse effects of atenoiol. Nervous System: reversible mental depression progressing to catatonia hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, decreased performance on europsychometrics; Cardiovascular: intensification of AV block (see CONTEAINDICATIONS); Gastrointestinal; mesenteric arterial thrombosis, ischemic colitis; Hematologic: agranulocytosis, nonthinombocytopenic purpura, thrombocytopenic purpura; Allergic: erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; Miscellaneous: reversible alopecia. Peyronie's disease.

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca.

reversible alopecia. Peyronie's disease.

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, olitis, and sclerosing serositis attributed to the beta-adrenergic receptor blocking agent, practolol. This syndrome has not been reported with TEMORETIC or TEMORMIN (atenolol).

Clinical Laboratory Test Findings: Clinically important changes in standard laboratory parameters were rarely associated with the administration of TEMORETIC. The changes in laborator parameters were not progressive and usually were not associated with clinical manifestations. The most common changes were increases in uric acid and decreases in serum potassium.

DOSAGE AND ADMINISTRATION: Initial dose should be one TEMORETIC 50 tablet once a day. If optimal response is not achieved, the dosage should be increased to one TEMORETIC 100 tablet once a day. Package insert should be consulted for dosage adjustments in cases of severe impairment of renal function.

once a day. Package insert should be consulted for dosage adjustments in cases of severe impairment of renal function.

HOW SUPPLIED: TENORETIC 50 Tablets (atenoiol 50 mg and chlorthalidone 25 mg), NDC 0310-011 (white, round, biconvex, uncoated tablets with ICI on one side and 115 on the other side, bisected) supplied in bottles of 100 tablets.

TENORETIC 100 Tablets (atenoiol 100 mg and chlorthalidone 25 mg), NDC 0310-0117 (white. rou biconvex, uncoated tablets with ICI on one side and 117 on the other side) are supplied in bottles of 100 tablets.

Particut from heat light and the side of the side

Protect from heat, light, and moisture. Dispense in well-closed, light-resistant container

Reference: 1. TENORETIC Evaluation Program, an open 28-day study of 26,892 hypertensive patients conducted by more than 7,000 physicians (data on file, ICI Pharma, Wilmington, Delaware physicians were requested to enter those patients needing more control than provided by



1 do not remain so, they may still be latently infected with HIV-1.

Farzadegan H, Polis MA, Wolinsky SM, et al: Loss of human immunodeficiency type 1 (HIV-1) antibodies with evidence of viral infection in asymptomatic homosexual men. *Ann Intern Med* 1988:108:785-790.

Intensive v less intensive hypertension treatment

Patients receiving systematic antihypertensive treatment designated as stepped care (SC) benefitted more than did those undergoing treatment provided by community sources of medical care, designated as referred care (RC) control group.

This conclusion, reached during the five-year, community-based Hypertension Detection and Follow-up Program (HDFP), was reiterated in a Posttrial Surveillance Study (PTS). The latter measured efficacy of SC and RC in treating hypertension and collected mortality data from the time HDFP ended at five years through the PTS, which extended the follow up to 8.3 years overall.

SC treatment lasted from 64 to 80 months while RC patients received treatment throughout the trial and posttrial periods or a total of 8.3 years. Fifteen percent fewer deaths occurred in the SC group than in the RC patients during the 8.3 years. Likewise, the five-year incidence of stroke, myocardial infarction, angina pectoris, and left ventricular hypertrophy declined in the SC group.

Hypertension Detection and Follow-up Program Cooperative Group: Persistence of reduction in blood pressure and mortality of participants in the Hypertension Detection and Follow-up Program. *JAMA* 1988;259:2113-2122.

Noninvasive treatment of gallbladder stones

Shock-wave lithotripsy, combined with chenodeoxycholic and ursodeoxycholic acid therapy, is a safe, effective treatment for dissolving radiolucent gallbladder calculi in certain patients.

Of the 175 patients who underwent this procedure in this study, 95% of those with one stone less than 20 mm in diameter experienced com-

plete resolution within 12 to 18 months after lithotripsy.

Sackmann M, Delius M, Sauerbruch T, et al: Shock-wave lithotripsy of gallbladder stones: The first 175 patients. N Engl J Med 1988;318:393-397.

Walking: A healthy exercise alternative

Besides benefitting the cardiovascular system, walking enhances weight loss by decreasing appetite; reduces anxiety and stress; increases high-density lipoprotein cholesterol levels; and slows the rate of bone loss.

Any prescribed exercise regimen, including walking, should be based on each person's aerobic capacity (VO₂) so as to prevent the level of exercise from being too easy or difficult. As such, most adults can reach heart rates above the training threshold during brisk walking. In addition, although walking with weights increases energy expenditure, the risks for elevated blood pressure and injury to the extremities make this type of exercise less desirable.

Rippe JM, Ward A, Porcari JP, et al: Walking for health and fitness. *JAMA* 1988;259:2720-2724

Human recombinant granulocyte colonystimulating factor and chemotherapy induced neutropenia

Human recombinant granulocyte colony-stimulating factor (rhG-CSF) serves as potent neutropenia prophylactic in patients receiving M-VAC chemotherapy. It also diminishes chemotherapy-related hematopoietic and oral toxicity.

Twenty-seven patients with transitional-cell carcinoma of the urothelium received rhG-CSF in doses of up to 60 μ g/kg of body weight daily. This treatment, administered after chemotherapy (methotrexate, doxorubicin, vinblastine, and cisplatin), reduced the number of days by 91% in which the absolute neutrophil count was $1000/\mu$ L or less. Furthermore, all patients were able to receive chemotherapy on the 14th day of the cycle, as originally planned.

Gabrilove JL, Jakubowski A, Scher H, et al: Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. N Engl J Med 1988;318:1414-1422

Diuretics and arrhythmia in hypertensives

Forty-four patients receiving 100 mg of hydrochlorothiazide a day showed no significant change in premature ventricular contractions, couplets, or ventricular tachycardia episodes. All had uncomplicated systemic hypertension.

Before diuretic therapy 20 patients exhibited class 2 to 5 ventricular ectopy; 17 did the same after treatment. Those with left ventricular hypertrophy did have increased ectopy when compared to baseline levels. Nevertheless, diuretic therapy did not adversely affect such arrhythmias.

Papademetriou V, Burris JF, Notargiacomo A, et al: Thiazide therapy is not a cause of arrhythmia in patients with systemic hypertension. Arch Intern Med. 1988:148:1272-1276.

Diabetic nephropathy and platelet inhibitor treatment

Dipyridamole and aspirin may stabilize renal function in insulin-dependent diabetics with nephropathy. Of the 28 patients participating in this ten-year prospective study, seven patients had a decline in urinary protein excretion after a mean treatment period of 4.3 years; 21 patients still had progressive nephropathy. Baseline C_{iot} values exceeded 50 mL/min per 1.73 m² in all seven of the stable group and nine of the 21 with progressive disease.

After three months' treatment, shortened platelet survival improved so that those with the progressive disease and those with progressive stable disease were equal.

By reducing platelet hypersensitivity and thromboxane production by platelet or renal tissue, renal function is stabilized and constrictor activity is decreased.

Donadio JV, Ilstrup DM, Holley KE, et al: Platelet-inhibitor treatment of diabetic nephropathy: A 10-year prospective study. *Mayo Clin Proc* 1988;63:3-15.

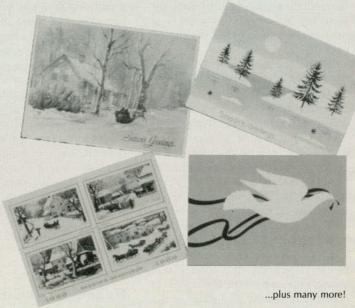


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Upjohn Introduces THE FIRST PRESCRIPTION MEDICATION PROVED EFFECTIVE FOR MALE PATTERN BALDNESS OF THE VERTEX





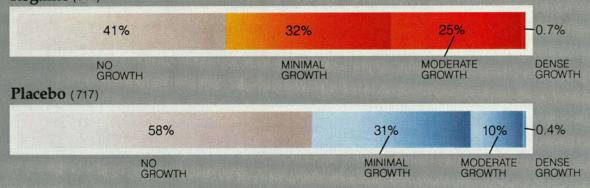
New ROGAINE Topical Solution 2% is the *first* prescription medication proved effective for male pattern baldness of the vertex. There was no evidence of effectiveness on frontal balding. Evidence of growth was demonstrated by objective hair counts and physician and patient evaluations of 1,431 patients in 27 centers across the United States. This landmark study was divided into two phases: The first phase compared ROGAINE with placebo in a double-blind protocol for four months; the second phase, non-placebo-controlled, evaluated continuous b.i.d. application of ROGAINE for an additional eight months.

PATIENTS' EVALUATIONS OF HAIR GROWTH OVER 12 MONTHS

Patients evaluated their response to ROGAINE Topical Solution (minoxidil 2%) or placebo each month for four months. They judged response to be no growth or minimal, moderate, or dense growth.

Four-Month Phase

PATIENT EVALUATION OF HAIR GROWTH AT FOUR MONTHS Rogaine (714)



Non-Placebo-Controlled Continuation Phase

In addition, after the placebo group was discontinued, continuous application of ROGAINE over an additional eight months was evaluated to determine growth.

PATIENT EVALUATION OF HAIR GROWTH AT 12 MONTHS Rogaine (619)



FOR THE FIRST TIME...OBJECTIVE EVIDENCE OF HAIR GROWTH IN MALE PATTERN BALDNESS OF THE VERTEX

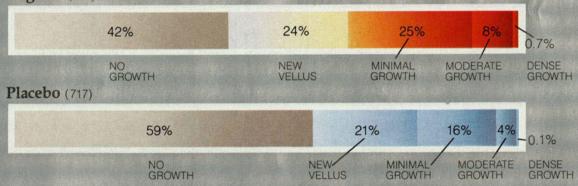
INVESTIGATORS' EVALUATIONS OF HAIR GROWTH OVER 12 MONTHS

Investigators evaluated patients on ROGAINE Topical Solution (minoxidil 2%) or placebo each month for four months. Response was judged to be no growth, new vellus (baby) hair, or minimal, moderate, or dense growth. (Photographs on following pages represent evaluations of minimal, moderate, and dense growth.) In addition, after the placebo group was discontinued, continuous application of ROGAINE over an additional eight months was evaluated to determine if nonvellus growth could be sustained.

Four-Month Phase

At the end of four months, 34% of patients treated with ROGAINE were evaluated by the investigators as showing nonvellus growth, while 20% showed nonvellus growth with placebo, a highly significant difference (P<.0005).

INVESTIGATOR EVALUATION OF HAIR GROWTH AT FOUR MONTHS Rogaine (714)



Non-Placebo-Controlled Continuation Phase

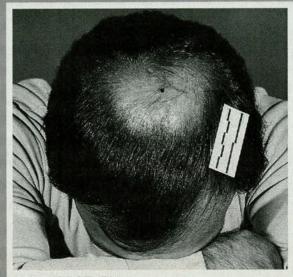
After 12 months, dense growth was observed in 8% of the 619 patients treated with ROGAINE, moderate growth in 31%, and minimal growth in 37%. Approximately one fourth of patients showed only vellus hair growth or no growth.

INVESTIGATOR EVALUATION OF HAIR GROWTH AT 12 MONTHS Rogaine (619)

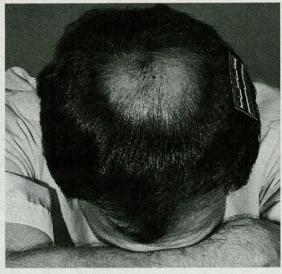


Please see next to last page for brief summary of prescribing information.

EXAMPLES OF MINIMAL, MODERATE, AND DENSE GROWTH AS EVALUATED BY INVESTIGATORS



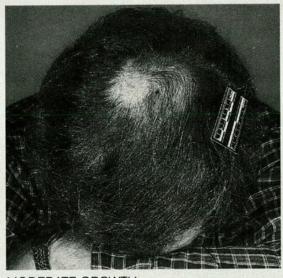
START OF STUDY



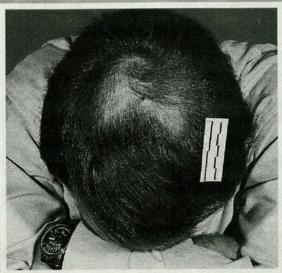
MINIMAL GROWTH



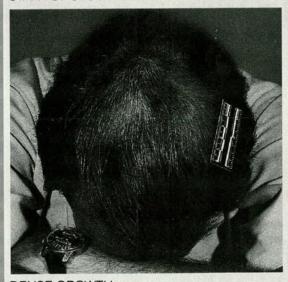
START OF STUDY



MODERATE GROWTH



START OF STUDY



DENSE GROWTH



TURN PAGE FOR HAIR COUNT EVALUATION

HAIR COUNTS CONFIRM HAIR GROWTH OVER 12 MONTHS

Monthly Hair Count Evaluation

Each month, nonvellus (normal) hairs were counted within a one-inch circle drawn on the vertex of the scalp of every patient, resulting in a mean nonvellus hair count.

Four-Month Phase

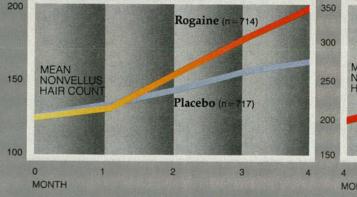
ROGAINE was shown to be significantly superior to placebo (P<.0005). Mean nonvellus hair count at the end of month 4 with ROGAINE was 192 versus 121 at baseline—an increase of 59%. Mean nonvellus hair count with placebo was 159 versus 120 at baseline—an increase of 33%.

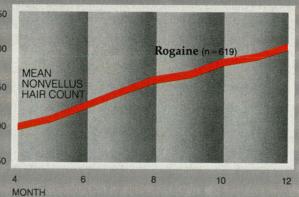
Non-Placebo-Controlled Continuation Phase

Continuous application of ROGAINE for an additional eight months resulted in sustained growth of nonvellus hair. Mean hair count increased 58%, from 192 at the four-month baseline to 304, confirming growth seen in the earlier phase of the study.

Four-Month Phase— Significant Growth With ROGAINE

Non-Placebo-Controlled Continuation Phase— Sustained Growth With ROGAINE





PATIENT CRITERIA FAVORING GROWTH

One cannot predict the response to ROGAINE in any given patient, but certain criteria favoring growth were seen during the study.

AGE

Younger patients showed better growth with ROGAINE.

DURATION OF BALDNESS

Patients balding less than ten years showed better growth with ROGAINE.

DIAMETER OF BALDING AREA

Patients with a balding area less than 10 cm (about 4 inches) showed better growth with ROGAINE.

LONG-TERM TREATMENT NECESSARY FOR SUSTAINED GROWTH

Daily b.i.d. applications of ROGAINE for four months or longer are usually necessary before evidence of growth is seen in most patients. When patients were followed for one year, hair growth continued.

Newly grown hair returns to the untreated state three to four months after cessation of therapy with ROGAINE.

Please see next to last page for brief summary of prescribing information.



TURN PAGE FOR INFORMATION ON SIDE EFFECTS

DATA FROM 5,891 PATIENTS SHOW A FAVORABLE SIDE-EFFECT PROFILE

INCIDENCE OF ADVERSE REACTIONS IS LOW

Dermatologic reactions were more common in the group treated with ROGAINE (5.27%) compared with placebo (3.44%). Otherwise, no individual reaction or reactions grouped by body systems appeared to be increased in the minoxidil-treated patients.

MEDICAL EVENT PERCENT OCCURRENCE BY BODY SYSTEM IN THE PLACEBO CONTROL CLINICAL TRIALS INVOLVING MINOXIDIL TOPICAL SOLUTION—ALL PATIENTS ENROLLED

MINOXIDIL SOLN PLACEBO N = 3510 (4-6 MONTHS) N = 2381 (4-

N = 2381 (4-6 MONTHS)

BODY SYSTEM	% OCC.	% occ.
RESPIRATORY	5.95	6.51
DERMATOLOGICAL	5.27	3.44
CARDIOVASCULAR	1.28	1.18

FEW PATIENTS DISCONTINUED THERAPY

At four months, 1.3% of patients treated with ROGAINE discontinued therapy because of side effects, compared with 1% of patients on placebo. After 12 months, a total of 3.1% of the patients treated with ROGAINE discontinued therapy because of side effects.

POTENTIAL ADVERSE EFFECTS

Extensive use of topical minoxidil has not revealed evidence that enough minoxidil is absorbed to have systemic effects. Greater absorption because of misuse or individual variability or unusual sensitivity could lead, at least theoretically, to a systemic effect, and patients need to be aware of this.

Experience with oral minoxidil when used for hypertension has shown the following major cardiovascular effects:

- salt and water retention, generalized and local edema
- pericardial effusion, pericarditis, tamponade
- tachycardia
- increased frequency of angina or new onset of angina

MINIMAL ABSORPTION RESULTS IN CONSISTENTLY LOW SERUM LEVELS OF MINOXIDIL

The failure to detect evidence of systemic effects during treatment reflects the poor absorption of topical minoxidil. In a study of patients with hypertension, mean minoxidil concentrations after 1 mL b.i.d. of 2% topical minoxidil (1.7 ng/mL) were 1/20 the concentrations seen after daily oral doses of 2.5 mg (32.8 ng/mL) or 5 mg (59.2 ng/mL).

Before starting a patient on ROGAINE, the physician should ascertain that the patient has a healthy, normal scalp. Local abrasion or dermatitis may increase absorption and hence increase the risk of side effects. Greater absorption because of misuse or individual variability or unusual sensitivity could lead, at least theoretically, to a systemic effect.

PATIENTS WITH CARDIOVASCULAR DISEASE

Patients with a history of underlying heart disease should be aware that adverse effects in them might be especially serious. Patients should be alerted to the possibility of tachycardia and fluid retention and should watch for, and be monitored for, increased heart rate and weight gain or other systemic effects. No drug interactions have been reported with ROGAINE but, theoretically, orthostatic hypotension may occur in patients taking guanethidine.

No Appreciable Pharmacologic Response in Untreated Hypertensives
A well-controlled multicenter study of patients with untreated hypertension was conducted to determine if ROGAINE had an effect on blood pressure or pulse rate or caused fluid accumulation. No appreciable pharmacologic response was seen after application of ROGAINE twice daily for four days.

Please see next to last page for brief summary of prescribing information.



THE FIRST AND ONLY STANDARDIZED FORMULATION FOR HAIR GROWTH

ROGAINE Topical Solution (minoxidil 2%) is a cosmetically elegant, consistent formulation. ROGAINE is attractively packaged with a choice of applicators designed to suit individual needs (see below). Each 60-mL bottle of ROGAINE provides enough medication for one month's therapy.

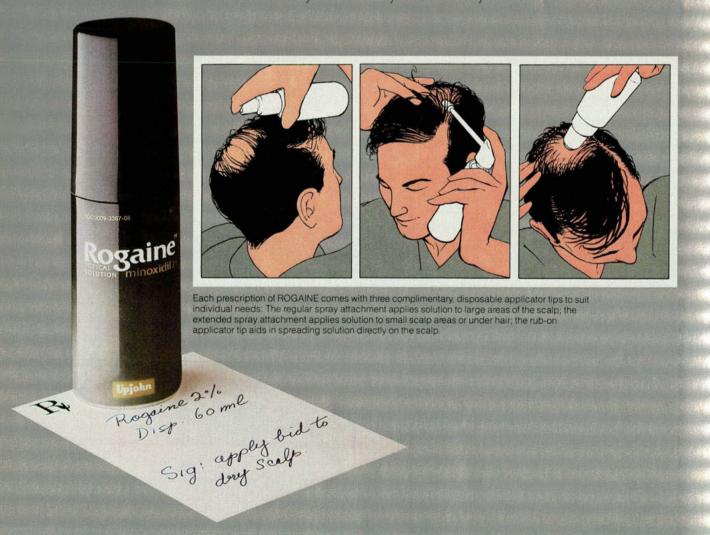
A STRICT REGIMEN: TWICE A DAY, EVERY DAY

One milliliter of ROGAINE should be applied to the total affected areas of the scalp twice daily. Hair and scalp should be dry before application.

CONTINUED USE NECESSARY

Patients must follow the regimen for ROGAINE faithfully and understand that twice-daily application for four months or longer may be required before hair growth can be expected. The studies also showed that further growth continued from month 5 through month 12. There was no evidence of effectiveness on frontal balding.

Continuous use is necessary to maintain growth. Newly grown hair returns to the untreated state three to four months after cessation of treatment.



CONTRAINDICATIONS

A history of hypersensitivity to minoxidil, propylene glycol or

WARNINGS

1 Need for normal scalp

Before starting treatment, make sure that the patient has a normal, healthy scalp. Local abrasion or dermatitis may increase absorption and hence the risk of side effects.

2. Potential adverse effects

Although extensive use of topical minoxidil has not revealed evidence that enough minoxidil is absorbed to have systemic effects, greater absorption due to misuse, individual variability or unusual sensitivity could, at least theoretically, produce a systemic effect.

Experience with oral minoxidil has shown the following major car-diovascular effects (Review the package insert for LONITEN® Tablets for details):

-salt and water retention, generalized and local edema

pericardial effusion, pericarditis, tamponade

tachycardia

 increased incidence of angina or new onset of angina
 Patients with underlying heart disease, including coronary artery disease and congestive heart failure, would be at particular risk of these potential effects. Additive effects could also emerge in patients being treated for hypertension.

Potential patients should have a history and physical, should be advised of potential risks and a risk benefit decision should be made. Heart patients should realize that adverse effects may be especially serious. Alert patients to the possibility of tachycardia and fluid retention, and monitor for increased heart rate, weight gain or other systemic effects.

PRECAUTIONS

General Precautions

Patients should be monitored one month after starting ROGAINE and at least every six months afterward. Discontinue ROGAINE if systemic effects occur. The alcohol base will burn and irritate the eye. If ROGAINE reaches sensitive surfaces (eg, eye, abraded skin and mucous membranes) bathe with copious cool water.

Avoid inhaling the spray.

Do not use in conjunction with other topical agents such as corticosteroids, retinoids and petrolatum or agents that enhance percutaneous absorption. ROGAINE is for topical use only. Each ml contains 20 mg minoxidil and accidental ingestion could cause adverse systemic effects.

Decreased integrity of the epidermal barrier caused by inflammation or disease of the skin, eg, excoriations, psoriasis or severe sunburn, may increase minoxidil absorption.

Patient Information

A patient information leaflet is included with each package and in the full product information.

Drug Interactions

No drug interactions are known. Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking

guanethidine.

Carcinogenesis, Mutagenesis and Impairment of Fertility
No carcinogenicity was found with topical application. There is a
suggestion that oral administration may be associated with an increased incidence of malignant lymphomas in female mice and hepatic nodules in male mice. In rats, there was a dose dependent reduction in conception rate.

Pregnancy Category C. ROGAINE should not be used by preg-

Labor and Delivery: The effects are not known.

Nursing Mothers: ROGAINE should not be administered. Pediatric Use: Safety and effectiveness have not been established under age 18.

ADVERSE REACTIONS

ROGAINE has been used by 3510 patients in placebo controlled trials. Except for dermatologic events, which were more common in the minoxidil group, no individual reaction or body system grouping seemed to be increased in the minoxidil treated group.

Medical Event Percent Occurrence By Body System In The Placebo Control Clinical Trials Involving Minoxidil Topical Solution — All Patients Enrolled

	N = 3 (4-6 m	dil Soln 3510 onths)	Placebo N = 2381 (4-6 months)		
BODY SYSTEM	PATS.	% 0CC.	PATS.	occ.	
RESPIRATORY (bronchitis, upper respiratory infection, sinusitis)	209	5.95	155	6.51	
DERMATOLOGICAL (irritant dermatitis, allergic contact dermatitis)	185	5.27	82	3.44	
GASTROINTESTINAL (diarrhea, nausea, vomiting)	120	3.42	117	4.91	
NEUROLOGY (headache, dizziness, faintness, lightheadedness)	90	2.56	71	2.98	
MUSCULOSKELETAL (fractures, back pain, tendinitis)	76	2.17	43	1.81	
CARDIOVASCULAR (edema, chest pain, blood pressure increases/decreases, palpitations, pulse rate increases/decreases)	45	1.28	28	1.18	
ALLERGY (non-specific allergic reactions, hives, allergic rhinitis, facial swelling, and sensitivity)	36	1.03	15	0.63	
SPECIAL SENSES (conjunctivitis, ear infections, vertigo)	33	0.94	26	1.09	
METABOLIC-NUTRITIONAL (edema, weight gain)	21	0.60	19	0.80	
URINARY TRACT (urinary tract infections renal calculi urethritis)	16	0.46	15	0.63	
GENITAL TRACT (prostatitis, epididymitis)	16	0.46	10	0.42	
PSYCHIATRIC (anxiety, depression, fatigue)	10	0.28	21	0.88	
HEMATOLOGY (lymphadenopathy, thrombocytopenia)	8	0.23	6	0.25	
ENDOCRINE	3	0.09	4	0.17	

Patients have been followed for up to 5 years and there has been no change in incidence or severity of reported reactions.

Additional events reported in postmarketing clinical experience include: eczema, hypertrichosis, local erythema, pruritus, dry skin/scalp flaking, sexual dysfunction, visual disturbances including decreased visual acuity, exacerbation of hair loss, alopecia.

DOSAGE AND ADMINISTRATION

Hair and scalp should be dry before application. 1 ml should be applied to the total affected areas twice daily. Total daily dose should not exceed 2 ml. If the fingertips are used to facilitate drug application, wash the hands afterwards.

HOW SUPPLIED

60 ml bottle with multiple applicators NDC 0009-3367-05 Caution: Federal law prohibits dispensing without a prescription.



ROSaine TOPICAL SOLUTION SOLUTION SOLUTION Minoxidil 2%



THE FIRST PRESCRIPTION MEDICATION
PROVED EFFECTIVE
FOR MALE PATTERN BALDNESS
OF THE VERTEX

Upjohn

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