Once-daily dosing of sustained-release diltiazem capsules in mild-to-moderate hypertension

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The safety and efficacy of a once-a-day regimen of sustained-release diltiazem capsules was assessed in 38 patients with essential hypertension (supine diastolic blood pressure, 95 to 114 mm Hg). After patients were withdrawn from previous antihypertensive therapy for four weeks, the dosage was titrated to the optimal diltiazem dose to produce a supine diastolic blood pressure <90 mm Hg or a drop ≥ 10 mm Hg from baseline pressures. They were maintained on that dosage for a total of eight weeks. A daily monotherapeutic diltiazem dose of 360 mg was required for 60% of the patients. The goal pressure was achieved for 53%, 67%, and 56% of patients at weeks 12, 16, and 20, respectively. One-third of the patients achieved the goal pressure at all three evaluations. Mean reductions in systolic and diastolic blood pressures, mean arterial pressure, and heart rate were significant ($P < 0.001$) at weeks 12, 16, and 20 in both supine and upright positions. The overall mean reduction in supine diastolic blood pressure was 9.2 mm Hg ($P < 0.0001$). Compliance was 99%. Overall, diltiazem produced no clinically significant adverse effects. Thus, in a sustained-release form, with a once-daily dosing regimen, diltiazem was effective and well tolerated as monotherapy for mild-to-moderate essential hypertension in a significant number of patients.

For many years, antihypertensive regimens have included a peripheral vasodilator. A relatively new class of vasodilator, calcium channel blockers, which previously had been used for treatment of angina pectoris, now has been proved effective in the management of mild-to-moderate essential hypertension.¹⁻³ Calcium channel blockers, such as diltiazem, also have been recognized to have a fairly benign side-effect profile, which makes them potential first-line drugs for the treatment of hypertension.

In sustained-release form, diltiazem is formulated for dosing twice a day; however, the duration of the pharmacologic effect of a drug does not necessarily correlate with its apparent pharmacokinetics.⁴ Because of this assumption and because noncompliance with hypertension therapy is so prevalent, the present study was designed to assess the efficacy and safety of a once-daily dosage regimen with 12-hour sustained-release diltiazem capsules for the management of mild-to-moderate hypertension.

Materials and methods

Patients

Each patient had essential hypertension with a stable resting supine diastolic pressure of 95 to 114 mm Hg, which varied no more than 7 mm Hg between visits. The demographics for the patient group are shown in Table 1.

Exclusion criteria

Patients were excluded from the study for these

TABLE 1. DEMOGRAPHIC SUMMARY OF STUDY SUBJECTS (N=38).

Sex	
Male	20
Female	18
Race	
Black	2
White	36
Smoker	
Yes	9
No	29
Family history of hypertension	
Yes	30
No	6
Unknown by patient	2
Duration of hypertension (yr)*	9.3 ± 9.2
Age (yr)	50.5 ± 12.0
Height (in)	
Men	68.9 ± 3.5
Women	62.9 ± 1.9
Weight (lb)	
Men	202.5 ± 41.6
Women	166.6 ± 40.4

*Four patients reported the duration of their hypertension as unknown.

reasons: significant cardiovascular disease other than essential hypertension, such as heart block greater than first degree or sick sinus syndrome; impaired renal function (serum creatinine value) >2 mg/dL); significant hepatic, endocrinous, metabolic, or neurologic disease; any condition known to affect the assimilation of drugs; abuse of alcohol or other drugs; hypersensitivity to diltiazem; or pregnancy. During the course of the study, no changes were made in patients' lifestyle, diet, or use of medications. All patients were required to provide informed consent. No medications known to affect blood pressure were permitted.

Drug administration

Diltiazem was administered as a 120-mg, sustained-release capsule in a single-blind, unrandomized fashion. Patients were unaware of whether they were receiving an active drug or a placebo. An initial placebo washout period of four to six weeks was used to verify the stable baseline supine diastolic pressure (95 to 114 mm Hg). Patients received a placebo identical in appearance to the diltiazem capsule given later.

After the washout, a 12-week titration period was initiated, and the dosage was adjusted to 120 mg, 240 mg, or 360 mg per day until one of the following occurred: The goal blood pressure was reached, maximum dose was achieved, or adverse effects limited further upward titration. Dosage adjustments were made at the end of weeks 4, 8, and

12 during the titration period. The titration phase was followed by an eight-week evaluation phase, during which the patient continued on with the determined optimal dosage.

Measurements

Goal blood pressure response was defined as a stable reduction in supine diastolic blood pressure ≥ 10 mm, or a reduction to <90 mm Hg for supine diastolic blood pressure. Upon entry into the study, each patient underwent a complete physical examination. An ECG was recorded, and a complete blood cell count (CBC), Sequential Multiple Analyzer Computerized (SMAC), and urinalysis were performed.

During the washout phase, patients were seen weekly for blood pressure measurements until the supine diastolic pressures obtained on two consecutive visits were in the range of 95 to 114 mm Hg and varied no more than 7 mm Hg from visit to visit. The same measurements were made every other week during the titration phase. Additional ECGs were obtained at weeks 2, 6, and 10, and a CBC, SMAC, and urinalysis were performed at the end of week 12.

During the evaluation phase, the supine and upright blood pressures were measured and ECGs were obtained at weeks 16 and 20. Another complete laboratory and physical examination were performed at the end of week 20, which completed the evaluation phase.

All blood pressure measurements were made at the same time of day for each patient (20 to 26 hours after previous dosing). Supine and upright (immediate standing and standing 5 minutes) blood pressures were measured weekly during washout, every other week during titration, and at weeks 16 and 20 during evaluation. Additional safety assessments (based on adverse reaction reports) were made at each patient visit.

Statistical analysis

Comparisons were made among the results at the end of the placebo, titration, and evaluation phases. The efficacy parameters compared were systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate. A repeated measures analysis of variance was used to assess significant correlation between evaluations. If significant correlation was found, the Huynh-Feldt adjustment to the analysis of variance F test was made. Without significant correlation, the analysis was equivalent to a split-plot analysis of variance. Student's t-tests were performed to compare (1) baseline to end titration and to each evaluation and (2) end titration to each evaluation. In addi-

TABLE 2. BLOOD PRESSURE AND HEART RATE DATA.

Measurement		Mean $\pm$ SD			
		Baseline (N = 38)	Week 12 (N = 38)	Week 16 (N = 36)	Week 20 (N = 36)
Posture	Parameter*				
Supine	SBP	153.4 $\pm$ 12.4	145.9 $\pm$ 13.5	144.4 $\pm$ 14.5	145.7 $\pm$ 15.3
	DBP	99.34 $\pm$ 4.62	90.82 $\pm$ 8.83	89.42 $\pm$ 6.06	90.19 $\pm$ 9.44
	MAP	117.36 $\pm$ 6.38	109.17 $\pm$ 8.59	107.74 $\pm$ 7.46	108.69 $\pm$ 9.32
	HR	74.38 $\pm$ 9.19	74.38 $\pm$ 9.19	74.15 $\pm$ 9.34	69.75 $\pm$ 10.73
Immediate standing	SBP	145.9 $\pm$ 12.7	138.3 $\pm$ 14.0	135.2 $\pm$ 15.2	133.3 $\pm$ 13.0
	DBP	95.28 $\pm$ 7.60	90.53 $\pm$ 9.64	87.61 $\pm$ 8.11	86.47 $\pm$ 11.42
	MAP	112.15 $\pm$ 8.49	106.44 $\pm$ 9.76	103.48 $\pm$ 8.45	102.07 $\pm$ 10.44
	HR	80.9 $\pm$ 10.4	80.47 $\pm$ 12.48	78.61 $\pm$ 10.85	78.78 $\pm$ 12.29
Standing 5 minutes	SBP	149.3 $\pm$ 14.1	142.0 $\pm$ 13.9	139.2 $\pm$ 14.6	140.3 $\pm$ 13.2
	DBP	96.91 $\pm$ 7.28	91.55 $\pm$ 10.37	89.69 $\pm$ 7.21	89.78 $\pm$ 10.06
	MAP	114.36 $\pm$ 8.72	108.37 $\pm$ 10.35	106.20 $\pm$ 8.79	106.62 $\pm$ 9.76
	HR	79.32 $\pm$ 8.86	76.63 $\pm$ 13.29	80.00 $\pm$ 10.04	79.67 $\pm$ 11.60

*SPB = systolic blood pressure; DPB = diastolic blood pressure; MAP = mean arterial pressure; and HR = heart rate.

Note: Compared with baseline values, all blood pressure changes were significant ($P < 0.001$) at weeks 12, 16, and 20.

tion, the percentage of patients achieving goal pressure reduction at each evaluation was determined, and 95% confidence intervals were constructed.

Results

Patient disposition

From a total of 44 patients enrolled in this study, 38 (20 men, 18 women) were evaluated for both safety and efficacy. The mean age was 50 years. Of the 44 participants, three were dropped from the study for administrative reasons and two because of intercurrent illnesses. One patient withdrew after reporting arm pain and edema. Two additional patients were withdrawn after week 12 because of diastolic blood pressures >114 mm Hg. Twenty-seven patients were screened but not enrolled because they did not meet the admission blood pressure requirements.

Therapy

Goal blood pressure (defined as either <90 mm Hg supine diastolic blood pressure or a ≥ 10 mm Hg drop in supine diastolic blood pressure) was met by 53%, 67%, and 56% of the patients at weeks 12, 16, and 20, respectively. One-third of the patients achieved goal at all three evaluations. Blood pressure and heart rate data at baseline and for weeks 12, 16, and 20 are shown in Table 2.

Mean reductions in systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate in all patients were significant at weeks 12, 16, and 20 in both the supine and upright positions ($P < 0.001$). For all 38 patients, the overall mean reduction in supine diastolic blood pressure

from baseline to week 20 was 9.2 mm Hg ($P < 0.0001$).

The titration scheme of 120, 240, and 360 mg/day of diltiazem resulted in a mean dose of 301.7 mg/day at the end of the evaluation phase (week 20). At the end of the study, 60% of the patients were at the maximum titrated dose of 360 mg/day. To the best of our knowledge, overall compliance during the active phase of the study was 99%, as calculated by the number of capsules returned by the patients at the end of the study.

No postural hypotension was reported, and no significant changes between baseline and subsequent evaluations for systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate were observed immediately upon standing.

There were no clinically significant laboratory changes. Diltiazem may be associated with slight but insignificant increases in triglyceride and alkaline phosphatase values, and a slight but insignificant decrease in the hemoglobin level.

Demographics

Baseline demographic characteristics were analyzed to determine the significance levels associated with them and to eliminate these factors as variables. Race, sex, or age had no detectable effect on blood pressure during diltiazem treatment.

Adverse reactions

Side effects reported by the patients were benign and were not considered to be clinically significant. The most common adverse events were edema, as-

thenia (weakness and fatigue), pain (burning sensation in foot, arm pain, leg cramp, general complaint of pain), headache, vertigo, insomnia, and dizziness. None of these events was considered to be serious, and all of the patients recovered during the course of the study.

Discussion

Calcium channel antagonists, by interfering with the influx of intracellular calcium into vascular smooth muscle, produce a vasodilation that is effective in controlling both angina^{5,6} and hypertension.^{1-3,7} Diltiazem also has been shown to improve exercise tolerance.⁸ The drug has not been associated with compromises in renal perfusion and function or left ventricular and diastolic pressure, or with orthostatic hypotension.⁹ It also has been shown to have a clinically insignificant adverse effect profile.⁹

Despite a short plasma elimination half-life of 3 to 4.5 hours, administration of diltiazem can be controlled with a sustained-release capsule to extend the bioavailability to 12 hours. The duration of the pharmacologic effect of many antihypertensive agents (beta-blockers, diuretics) outlasts appreciable blood levels. It was this assumption that prompted us to gain further clinical experience with a sustained-release diltiazem capsule in a once-daily dosing regimen. In a previous study,³ both supine and standing diastolic blood pressures dropped 10 mm Hg after 12 weeks of active treatment with once-a-day diltiazem dosing.

Our study did support the hypothesis that the antihypertensive effect of diltiazem could carry a patient through a 24-hour period with once-daily dosing. At the end of the study, 57% of the patients were being maintained at goal blood pressure. Despite the titration to the maximum single dose of 360 mg/day for 60% of the patients, no significant adverse effects or laboratory changes were reported. The once-daily dosing schedule also was convenient for the patients, as evidenced by the 99% compliance figure.

Conclusions

Because of the wide variety of cardiovascular actions attributable to diltiazem, it is in several populations and disease states simultaneously. The lack of significant atrioventricular nodal depression with diltiazem and the favorable effect on exercise tolerance, in conjunction with a benign side-effect profile, make diltiazem, especially with a once-daily dosing regimen, either as monotherapy or combined therapy, a useful option for practitioners treating hypertension and angina in a wide variety of patients.

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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 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 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.

Ischemic Heart Disease: Although not yet reported with atenolol 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 carefully observed and should be advised to limit physical activity to a minimum. 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 beta₁-selectivity is not absolute, the lowest possible dose of TENORETIC should be used and a beta₂-stimulating 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. If 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 become manifest during chlorthalidone administration.

Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis and from whom TENORETIC therapy is to be withdrawn should be 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 therapy.

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 urine 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, lethargy, 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 foods with a high potassium content.

Any chloride deficit 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 may potentiate the action of other antihypertensive agents used concomitantly. Patients treated with 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 sufficient to preclude the therapeutic effectiveness of norepinephrine. Thiazides may increase the responsiveness to tubocurarine.

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 of clonidine.

Other Precautions: In patients receiving thiazides, sensitivity reactions may occur with or without a 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 the postsympathectomy patient.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration 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 maximum 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 cytogenetic test and the Salmonella typhimurium 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 the maximum recommended human dose) was unaffected by atenolol administration.

Use in Pregnancy: Pregnancy Category C. TENORETIC (atenolol and chlorthalidone) was studied for teratogenic potential in the rat and rabbit. Doses of 10, 100 and 300 mg/kg/day were administered orally to pregnant rats, with no teratologic effects observed. Two studies were conducted in rabbits. In 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 were 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.

Atenolol—Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more 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 are no adequate and well-controlled studies in pregnant women.

Chlorthalidone—Thiazides cross the placental barrier and appear in cord blood. The use of chlorthalidone and related drugs in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, 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 most 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 placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for 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):

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%), light-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:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (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 use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

Chlorthalidone: Cardiovascular: orthostatic hypotension; Gastrointestinal: anorexia, gastric irritation, vomiting, cramping, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, CNS: vertigo, paresthesias, xanthopsia; Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; Hypersensitivity: purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis, cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis); Miscellaneous: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness. Clinical trials of TENORETIC conducted in the United States (89 patients treated with TENORETIC) revealed no new or 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 potential adverse effects of atenolol. 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 neuropsychometrics. Cardiovascular: intensification of AV block (see CONTRAINDICATIONS); Gastrointestinal: mesenteric arterial thrombosis, ischemic colitis; Hematologic: agranulocytosis, nonthrombocytopenic 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, otitis, and sclerosing sokeritis attributed to the beta-adrenergic receptor blocking agent, practolol. This syndrome has not been reported with TENORETIC or TENORMIN (atenolol).

Clinical Laboratory Test Findings: Clinically important changes in standard laboratory parameters were rarely associated with the administration of TENORETIC. The changes in laboratory 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 TENORETIC 50 tablet once a day. If optimal response is not achieved, the dosage should be increased to one TENORETIC 100 tablet once a day. Package insert should be consulted for dosage adjustments in cases of severe impairment of renal function.

HOW SUPPLIED: TENORETIC 50 Tablets (atenolol 50 mg and chlorthalidone 25 mg), NDC 0310-0115 (white, round, biconvex, uncoated tablets with ICI on one side and 115 on the other side, bisected) are supplied in bottles of 100 tablets.

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

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 monotherapy.