



IN HYPERTENSION

**When a complex regimen reduces compliance...  
It's time for TENORETIC.**

One-tablet-a-day TENORETIC is the simplest regimen available. It's easy, convenient therapy that works round-the-clock to effectively lower blood pressure without added tablets or added side effects that discourage patient compliance.

ONE TABLET A DAY  
**Tenoretic**<sup>®</sup>

Each tablet contains:  
**TENORMIN**<sup>®</sup> (atenolol) 50 mg or 100 mg  
and chlorthalidone 25 mg

**For your difficult-to-manage hypertensive.**

*TENORETIC is not indicated for the initial therapy of hypertension. See next page for brief summary of prescribing information.*

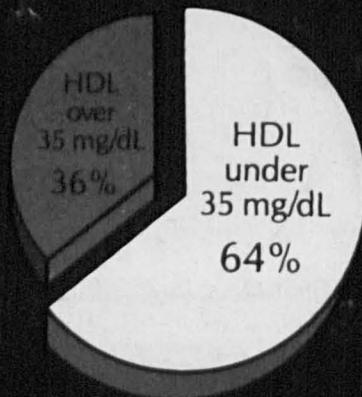
240  
TOTAL

<35  
HDL

Low HDL with elevated  
LDL and triglycerides:  
A common denominator of  
many heart attack victims

*Mixed hyperlipidemias—elevated cholesterol and triglycerides—are common among heart attack victims,<sup>1</sup> and nearly two thirds of people who developed myocardial infarction in the PROCAM Trial had a low (< 35 mg/dL) baseline level of HDL cholesterol.<sup>2</sup> LOPID<sup>®</sup> (gemfibrozil) is not indicated for the treatment of patients with low HDL cholesterol as their only lipid abnormality.*

HEART ATTACK PATIENTS  
(PROCAM TRIAL)<sup>2</sup>



# A powerful case for

# LOPID<sup>®</sup>



BID

# (gemfibrozil) 600-mg Tablets

LOPID is indicated for reducing the risk of coronary heart disease in type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

## Raised low HDL 25%

—in patients whose baseline HDL was < 35 mg/dL and median baseline LDL was 186 mg/dL in the landmark Helsinki Heart Study (HHS).<sup>3</sup>

## Reduced heart attack incidence up to 62%\*

—in these HHS patients.<sup>3</sup> Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).<sup>3</sup>

## RAISES HDL, LOWERS LDL AND TRIGLYCERIDES DRAMATICALLY REDUCES HEART ATTACK

Contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil. LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis. Caution should be exercised when anticoagulants are given in conjunction with LOPID.

\*Defined as a combination of definite coronary death and/or definite myocardial infarction.  
P = .013; 95% CI 13.3 to 111.5.

**References** 1. Goldstein JL, Hazzard WR, Schrott HC, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973;52:1533-1543.  
2. Assmann G, Schulte H. PROCAM-Trial: Prospective Cardiovascular Munster Trial. Zurich: Panscientia Verlag; 1986:8-9. 3. Data on file, Medical Affairs Dept, Parke-Davis.

Please see last page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

## Lopid® (Gemfibrozil Capsules and Tablets)

Before prescribing, please see full prescribing information. A Brief Summary follows.

**CONTRAINDICATIONS.** 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).
3. Hypersensitivity to gemfibrozil.

**WARNINGS.** 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group,  $p=0.056$ ).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group ( $p=0.06$ ; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

**PRECAUTIONS.** 1. **Initial Therapy**—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy**—Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant ( $p=0.1$ ). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

## Lopid® (Gemfibrozil Capsules and Tablets)

from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally

during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children**—Safety and efficacy in children have not been established.

**ADVERSE REACTIONS.** In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2%

(23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

**Gallbladder surgery** was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests and hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

**CAUSAL RELATIONSHIP PROBABLE:** *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

**CAUSAL RELATIONSHIP NOT ESTABLISHED:** *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

**DOSAGE AND ADMINISTRATION.** The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

**MANAGEMENT OF OVERDOSE.** While there has been no reported case of overdose, symptomatic supportive measures should be taken should it occur.

**References:** 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed. McGraw-Hill, 1983, Chap. 30, pp 622-642.

**Caution**—Federal law prohibits dispensing without prescription.

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PD-56-JA-676-B(1031)

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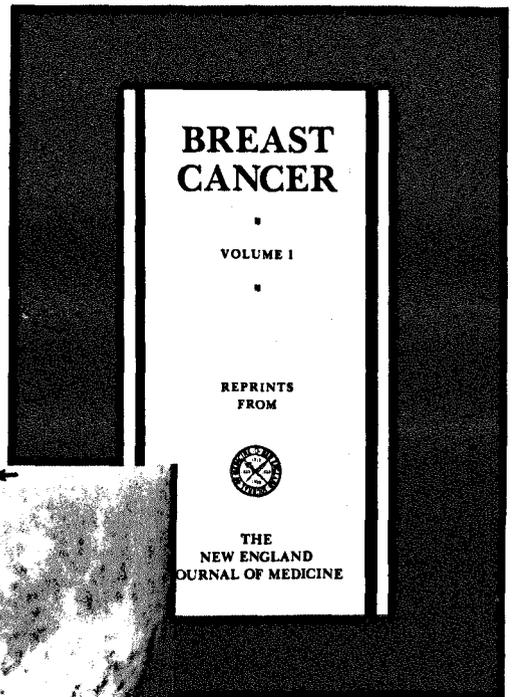
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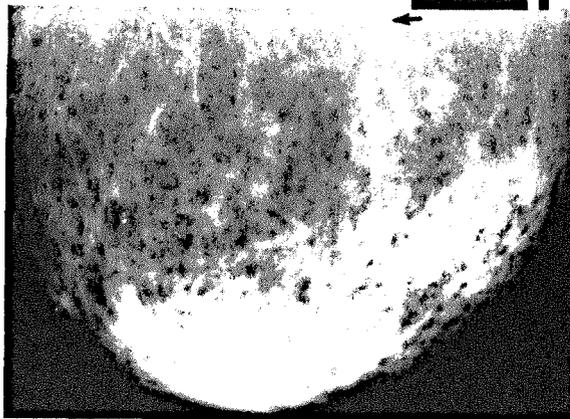
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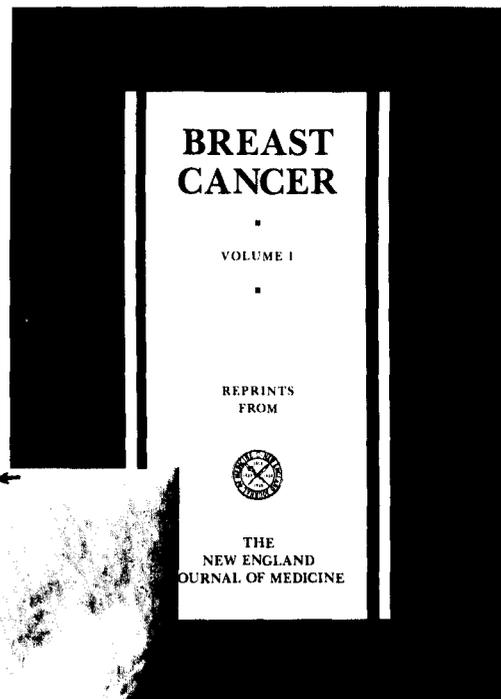
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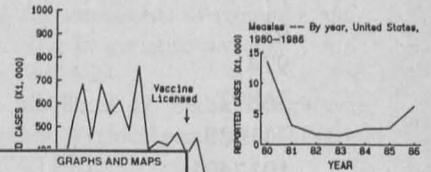
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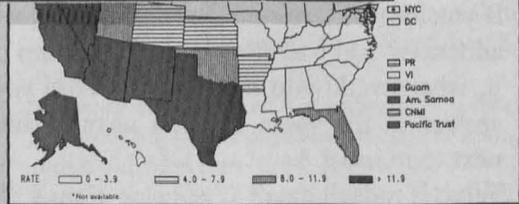
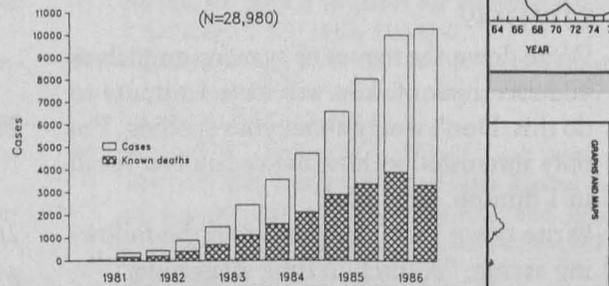
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# Your Best Lines of Defense Against Disease are

MEASLES (rubeola) — By year, United States, 1950-1986



ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) — Cases and known deaths, by 6 month periods of report to CDC, United States, 1981-1986



| Disease               | Total   | Age group |       |       |         |         |         |         |       |        |       |       |  |
|-----------------------|---------|-----------|-------|-------|---------|---------|---------|---------|-------|--------|-------|-------|--|
|                       |         | 1-4       | 5-9   | 10-14 | 15-19   | 20-24   | 25-29   | 30-39   | 40-49 | 50-59  | 60+   |       |  |
| AIDS                  | 12,032  | 69        | 72    | 73    | 5       | 11      | 614     | 2,190   | 4,028 | 2,546  | 950   | 262   |  |
| Cholera               | 23      | —         | 1     | 2     | 2       | —       | —       | 2       | 18    | —      | 1     | —     |  |
| Diphtheria            | —       | —         | —     | —     | —       | —       | —       | —       | —     | —      | —     | —     |  |
| Enteritis             | 900,887 | 1         | 2,224 | 8,038 | 215,818 | 337,711 | 584,580 | 114,286 | 1     | 34,202 | —     | —     |  |
| Measles A             | 73,430  | 1,185     | 2,520 | 6,187 | 9,933   | 9,200   | 4,214   | 4,607   | 1,584 | 1,041  | —     | —     |  |
| Measles B             | 28,017  | 119       | 149   | 134   | 203     | 224     | 170     | 370     | 2,033 | 1,101  | 1,301 | 1,819 |  |
| Measles total (A+B)   | 101,447 | 1,304     | 2,669 | 6,321 | 10,136  | 9,424   | 4,384   | 4,977   | 3,617 | 2,382  | 2,302 | 3,620 |  |
| Scarlet fever         | 3,940   | 15        | 123   | 334   | 317     | 317     | 878     | 777     | 782   | 701    | 1,433 | 2,287 |  |
| Whooping cough        | 6,782   | 339       | 1,747 | 676   | 1,342   | 1,336   | 264     | 179     | 125   | 231    | 61    | 62    |  |
| Measles-rubeola total | 2,384   | 608       | 843   | 162   | 127     | 234     | 142     | 75      | 125   | 301    | 301   | 203   |  |
| Scarlet fever         | 2,317   | 644       | 825   | 163   | 127     | 234     | 142     | 75      | 125   | 301    | 301   | 203   |  |
| Whooping cough        | 7,790   | 142       | 589   | 1,768 | 2,675   | 1,535   | 177     | 34      | 140   | 441    | 261   | 283   |  |
| Polio (wild-type)     | 4,199   | 1,520     | 504   | 272   | 144     | 152     | —       | —       | —     | —      | —     | —     |  |
| Polio (total)         | 10      | —         | 3     | —     | —       | —       | —       | —       | —     | —      | —     | —     |  |
| Polio (total)         | 4,209   | 1,520     | 507   | 272   | 144     | 152     | —       | —       | —     | —      | —     | —     |  |
| Polio (total)         | 10      | —         | 3     | —     | —       | —       | —       | —       | —     | —      | —     | —     |  |
| Polio (total)         | 4,209   | 1,520     | 507   | 272   | 144     | 152     | —       | —       | —     | —      | —     | —     |  |
| Polio (total)         | 10      | —         | 3     | —     | —       | —       | —       | —       | —     | —      | —     | —     |  |
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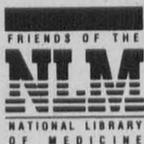
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# ONE TABLET A DAY Tenoretic® (atenolol and chlorthalidone)

(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

**INDICATIONS AND USAGE:** TENORETIC is indicated in 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:** Symptomatic 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 patients who have congestive heart failure controlled by digitalis and/or 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 digitized 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:** 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. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TENORETIC therapy abruptly even in patients treated only for hypertension.

**Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS.** Because of its relative beta<sub>1</sub>-selectivity, however, TENORETIC may be used with caution in patients with bronchospastic disease who do not respond or for whom alternate, other antihypertensive treatment. Since beta<sub>1</sub>-selectivity is not absolute, the lowest possible dose of TENORETIC should be used and a beta<sub>2</sub>-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:** It is not advisable to withdraw beta-adrenergic blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

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).

**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. At recommended doses 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 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: 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, dizziness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Measurement of potassium levels is appropriate especially in elderly patients, those receiving digitalis preparations for cardiac failure, patients whose dietary intake of potassium is abnormally low, or those suffering from gastrointestinal complaints.

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, 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 postoperative activation of systemic lupus erythematosus has been reported. The antihypertensive effects of thiazides may be enhanced in the postsympathectomy patient.

While taking beta blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

**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, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose\*, did not indicate a carcinogenic potential of atenolol. A third (24 month) rat study, employing doses of 500 and 1,500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose\*) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), in vivo cytogenetics test (Chinese hamster) or Ames test (*S typhimurium*).

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.

**Animal Toxicology Studies:** Studies were conducted in rats and dogs using TENORETIC doses up to 12.5 mg/kg/day (atenolol/chlorthalidone 10/2.5 mg/kg/day) — approximately five times the maximum recommended human antihypertensive dose\*. There were no functional or morphological abnormalities resulting from dosing either compound alone or together other than minor changes in heart rate, blood pressure and urine chemistry which were attributed to the known pharmacologic properties of atenolol and/or chlorthalidone.

Chronic studies of atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at tested dose levels (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose\*) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg/kg/day (150 and 75 times the maximum recommended human antihypertensive dose\*, respectively).

**Use in Pregnancy: Pregnancy Category C.** TENORETIC was studied for teratogenic potential in the rat and rabbit. Doses of atenolol/chlorthalidone of 8/2, 80/20, and 240/80 mg/kg/day were administered orally to pregnant rats with no teratologic effects observed. Two studies were conducted. In the first study, pregnant rabbits were dosed with 8/2, 80/20, and 160/40 mg/kg/day of atenolol/chlorthalidone. 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, doses of atenolol/chlorthalidone were 4/1, 4/2, and 20/5 mg/kg/day. No teratogenic or embryotoxic effects were demonstrated. It is concluded that the no-effect level for embryonic resorptions is 20/5 mg/kg/day of atenolol/chlorthalidone (approximately ten times the maximum recommended human dose\*). 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 antihypertensive 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 antihypertensive 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.

## TENORETIC® (atenolol and chlorthalidone)

**Nursing Mothers:** Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when atenolol is administered to a nursing woman. Clinically significant bradycardia has been reported in breast fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

**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 in the following table were derived 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.

|   | Volunteered (US Studies) |                     | Total-Volunteered and Elicited (Foreign + US Studies) |                     |
|---|--------------------------|---------------------|---|---------------------|
|   | Atenolol (n = 164) %     | Placebo (n = 206) % | Atenolol (n = 399) %                                  | Placebo (n = 407) % |
| <b>CARDIOVASCULAR</b>                       |                          |                     |   |                     |
| Bradycardia                                 | 3                        | 0                   | 3   | 0                   |
| Cold Extremities                            | 0                        | 0.5                 | 12  | 5                   |
| Postural Hypotension                        | 2                        | 1                   | 4   | 5                   |
| Leg Pain                                    | 0                        | 0.5                 | 3   | 1                   |
| <b>CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR</b> |                          |                     |   |                     |
| Dizziness                                   | 4                        | 1                   | 13  | 6                   |
| Vertigo                                     | 2                        | 0.5                 | 2   | 0.7                 |
| Light-Headedness                            | 1                        | 0                   | 3   | 13                  |
| Tiredness                                   | 0.6                      | 0.5                 | 26  | 13                  |
| Fatigue                                     | 3                        | 0                   | 6   | 5                   |
| Lrowsiness                                  | 1                        | 0                   | 3   | 0.7                 |
| Depression                                  | 0.6                      | 0.5                 | 12  | 9                   |
| Dreaming                                    | 0                        | 0                   | 3   | 1                   |
| <b>GASTROINTESTINAL</b>                     |                          |                     |   |                     |
| Diarrhea                                    | 2                        | 0                   | 3   | 2                   |
| Nausea                                      | 4                        | 1                   | 3   | 1                   |
| <b>RESPIRATORY (see Warnings)</b>           |                          |                     |   |                     |
| Wheeziness                                  | 0                        | 0                   | 3   | 3                   |
| Dyspnea                                     | 0.6                      | 1                   | 6   | 4                   |

**MISCELLANEOUS:** There have been reports of skin rashes and/or dry eye 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.

During postmarketing experience, the following have been reported in temporal relationship to the use of the drug: reversible alopecia, impotence, elevated liver enzymes and/or bilirubin, and thrombocytopenia.

**Chlorthalidone:** Cardiovascular: orthostatic hypotension; Gastrointestinal: anorexia, gastric irritation, vomiting, cramping, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; CNS: vertigo, parasthesias, xanthopsia; Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; Hypersensitivity: purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis); Lyle'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 cataplexy; hallucinations; an acute reversible syndrome characterized by disorientation in time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased concentration on neuropsychometrics; Cardiovascular: intensification of AV block (see CONTRAINDICATIONS); Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis; Hematologic: Agranulocytosis, purpura; Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; Miscellaneous: Pnyrom's disease.

There have been reports of a syndrome comprising psoriasis-like skin rash, conjunctivitis sicca, otitis, and sclerosing serositis 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.

**OVERDOSAGE:** No specific information is available with regard to overdosage and TENORETIC in humans. Treatment should be symptomatic and supportive and directed to the removal of any unabsorbed drug by induced emesis, or administration of activated charcoal. Atenolol can be removed from the general circulation by hemodialysis. Further consideration should be given to dehydration, electrolyte imbalance and hypotension by established procedures.

**Atenolol:** Overdosage with atenolol has been reported with patients surviving acute doses as high as 5 g. One death was reported in a man who may have taken as much as 10 g acutely.

The predominant symptoms reported following atenolol overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause, and bradycardia. Additionally, common effects associated with overdosage of any beta-adrenergic blocking agent are congestive heart failure, hypotension, bronchospasm, and/or hypoglycemia. Other treatment modalities should be employed at the physician's discretion and may include:

**BRADYCARDIA:** Atropine 1-2 mg intravenously. If there is no response to vagal blockade, give isoproterenol cautiously in refractory cases, a transvenous cardiac pacemaker may be indicated. Glucagon in a 10 mg intravenous bolus has been reported to be useful. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10 mg/h depending on response.

**HEART BLOCK (SECOND OR THIRD DEGREE):** isoproterenol or transvenous pacemaker.

**CONGESTIVE HEART FAILURE:** Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.

**HYPOTENSION:** Vasopressors such as dopamine or norepinephrine (levartrenolol). Monitor blood pressure continuously.

**BRONCHOSPASM:** A beta<sub>2</sub>-stimulant such as isoproterenol or terbutaline and/or aminophylline.

**HYPOGLYCEMIA:** Intravenous glucose.

**ELECTROLYTE DISTURBANCE:** Monitor electrolyte levels and renal function. Institute measures to maintain hydration and electrolytes.

Based on the severity of symptoms, management may require intensive support care and facilities for applying cardiac and respiratory support.

**Chlorthalidone:** Symptoms of chlorthalidone overdose include nausea, weakness, dizziness and disturbances of electrolyte balance.

**DOSEAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED (SEE INDICATIONS)**

Chlorthalidone is usually given at a dose of 25 mg daily. The usual initial dose of atenolol is 50 mg daily. Therefore, the initial dose should be one TENORETIC 50 tablet given once a day. If an optimal response is not achieved, the dosage should be increased to one TENORETIC 100 tablet given once a day.

When necessary, another antihypertensive agent may be added gradually beginning with 50 percent of the usual recommended starting dose to avoid an excessive fall in blood pressure.

Since atenolol is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function.

No significant accumulation of atenolol occurs until creatinine clearance falls below 35 mL/min/1.73m<sup>2</sup> (normal range is 100-150 mL/min/1.73m<sup>2</sup>); therefore, the following maximum dosages are recommended for patients with renal impairment.

| Creatinine Clearance (mL/min/1.73m <sup>2</sup> ) | Atenolol Elimination Half-life (h) | Maximum Dosage        |
|---|------------------------------------|-----------------------|
| 15-35   | 16-27                              | 50 mg daily           |
| <15   | >27                                | 50 mg every other day |

**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.

Store at controlled room temperature, 15°-30°C (59°-86°F). Dispense in well-closed, light-resistant containers.

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A business unit of ICI Americas Inc.  
Wilmington, Delaware 19877 USA

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