IN HYPERTENSION

LISINOPRIL IS POSITIVELY...

ONCE-DAILY

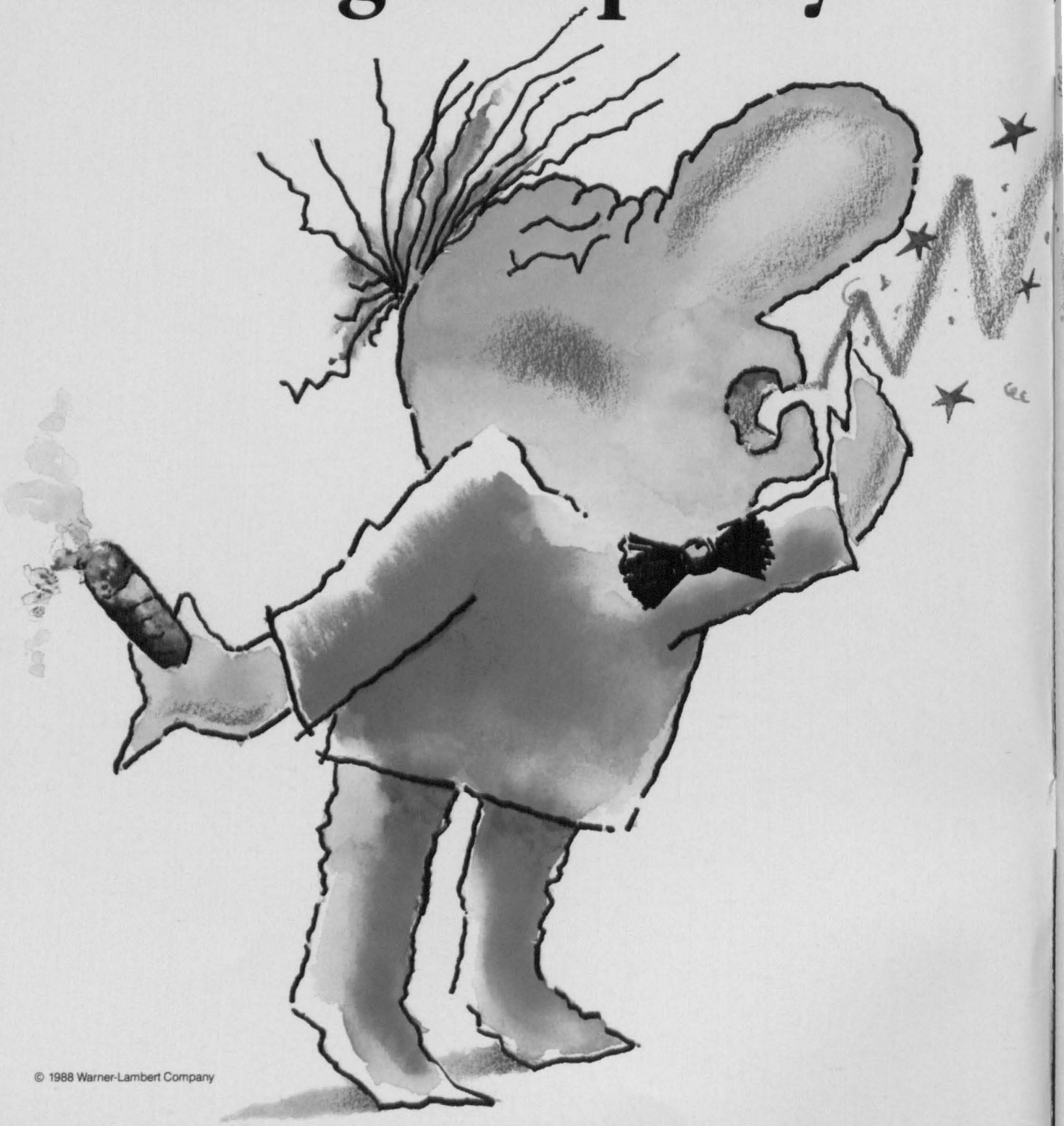
PRINIVIL®

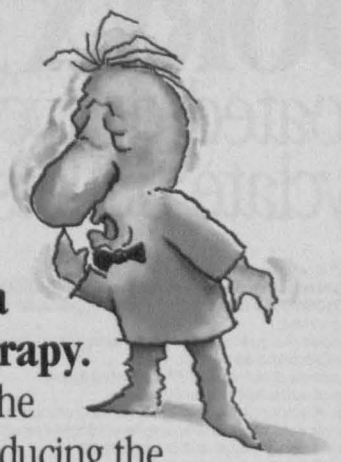
(LISINOPRIL/MSD)

Discovered and Developed by Merck Sharp & Dohme Research Laboratories

For a Brief Summary of Prescribing Information, please see the following page.

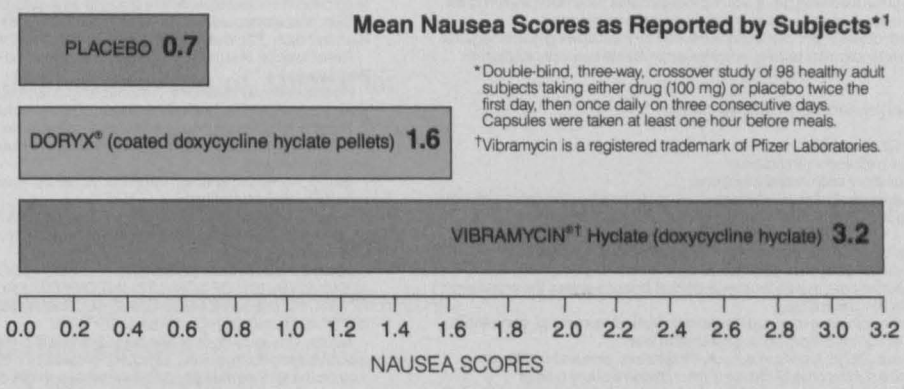
When he's not coughing, is his antibiotic making him queasy?





Bronchitis is difficult enough without the nausea that may sometimes accompany doxycycline therapy.

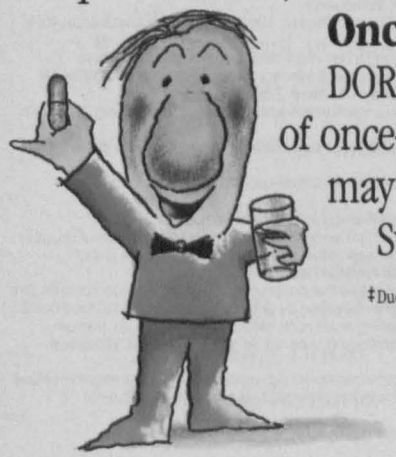
The pellets of DORYX, however, pass intact through the stomach and dissolve in the small intestine—reducing the potential for GI upset and nausea while providing all the benefits of doxycycline.[1]



*Double-blind, three-way, crossover study of 98 healthy adult subjects taking either drug (100 mg) or placebo twice the first day, then once daily on three consecutive days. Capsules were taken at least one hour before meals.

†Vibramycin is a registered trademark of Pfizer Laboratories.

The doxycycline in DORYX is active against such respiratory pathogens as *Streptococcus pneumoniae,*[2] *Hemophilus influenzae,*[2] *Mycoplasma pneumoniae,*[3] *and Chlamydia psittaci.*[4]



Once-a-day dosing

DORYX gives your bronchitis‡ patients the convenience of once-a-day dosing, to promote compliance. And DORYX may be taken with meals.

Switch to DORYX. For efficacy with excellent tolerability.

‡Due to susceptible organisms.

Doxycycline with a difference.

DORYX® Pellets

(coated doxycycline hyclate pellets) 100-mg Capsules

PARKE-DAVIS

Please see next page for brief summary of prescribing information.

DORYX® Pellets (coated doxycycline hyclate pellets) 100-mg Capsules

DORYX® (coated doxycycline hyclate pellets)
Before prescribing, please see full prescribing information. A Brief Summary follows.
INDICATIONS AND USAGE. Doxycycline is indicated in infections caused by the following microorganisms:

Rickettsiae (Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox and tick fevers).
Mycoplasma pneumoniae (PPLO, Eaton's agent).
Agents of psittacosis and ornithosis.
Agents of lymphogranuloma venereum and granuloma inguinale.
The spirochetal agent of relapsing fever (*Borrelia recurrentis*).

The following gram-negative microorganisms:

Haemophilus ducreyi (chancroid)
Yersinia pestis (formerly *Pasteurella pestis*)
Francisella tularensis (formerly *Pasteurella tularensis)*
Bartonella bacilliformis
Bacteroides species
Vibrio cholerae (formerly *Vibrio comma*)
Campylobacter fetus (formerly *Vibrio fetus*)
Brucella species (in conjunction with streptomycin)

Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended.

Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug:

Escherichia coli
Enterobacter aerogenes (formerly *Aerobacter aerogenes*)
Shigella species
Mima species and *Herellea* species
Haemophilus influenzae (respiratory infections)
Klebsiella species (respiratory and urinary infections)

Doxycycline is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriological testing indicates appropriate susceptibility to the drug:

Streptococcus species: Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organism has been demonstrated to be susceptible.

For upper respiratory infections due to group A beta-hemolytic streptococci, penicillin is the usual drug of choice, including prophylaxis of rheumatic fever.

Diplococcus pneumoniae. Staphylococcus aureus, (respiratory, skin and soft-tissue infections). Tetracyclines are not the drug of choice in the treatment of any type of staphylococcal infection.

When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of infections due to:

Treponema pallidum and *Treponema pertenue* (syphilis and yaws)
Listeria monocytogenes
Clostridium species
Bacillus anthracis
Fusobacterium fusiforme (Vincent's infection)
Actinomyces species

In acute intestinal amebiasis doxycycline may be a useful adjunct to amebicides.

In severe acne doxycycline may be useful adjunctive therapy.

Doxycycline is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence.

Inclusion conjunctivitis may be treated with oral doxycycline alone, or with a combination of topical agents.

Doxycycline is indicated for the treatment of uncomplicated urethral, endocervical or rectal infections in adults caused by *Chlamydia trachomatis.*

Doxycycline is indicated for the treatment of nongonococcal urethritis caused by *Chlamydia trachomatis* and *Ureaplasma urealyticum* and for the treatment of acute epididymo-orchitis caused by *Chlamydia trachomatis.*

Doxycycline is indicated for the treatment of uncomplicated gonococcal infections in adults (except for anorectal infections in men), the gonococcal arthritis-dermatitis syndrome and acute epididymo-orchitis caused by *N. gonorrhoeae.*

CONTRAINDICATIONS. The drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS. THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN). This adverse reaction is more common during long term use of the drugs but has been observed following repeated short term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has been noted in animals treated early in pregnancy. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking these drugs, the patient should be apprised of potential hazard to the fetus.

As with other tetracyclines, doxycycline forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

PRECAUTIONS. As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

All infections due to group A beta-hemolytic streptococci should be treated for at least 10 days.

Laboratory tests: In venereal disease when coexistent syphilis is suspected, dark-field examination should be done before treatment is started and the blood serology repeated monthly for at least 4 months.

In long term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic studies should be performed.

Drug interactions: Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracyclines in conjunction with penicillin.

For concomitant therapy with antacids or iron-containing preparations and food see "Dosage and Administration" section.

Carcinogenesis, mutagenesis, impairment of fertility: Long term studies are currently being conducted to determine whether tetracyclines have carcinogenic potential. Animal studies conducted in rats and mice have not provided conclusive evidence that tetracyclines may be carcinogenic or that they impair fertility. In two mammalian cell assays (L51784 mouse lymphoma and Chinese hamster lung cells *in vitro*) positive responses for mutagenicity occurred at concentrations of 60 and 10 mcg/mL respectively. In humans no association between tetracyclines and these effects have been made.

Pregnancy: Pregnancy Category D (See Warnings section).

Nursing mothers: Tetracyclines are present in the milk of lactating women who are taking a drug in this class. Because of the potential for serious adverse reactions in nursing infants from the tetracyclines, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother (see Warnings section).

Pediatric use: See Warnings and Dosage and Administration sections.

ADVERSE REACTIONS. Due to oral doxycycline's virtually complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline class. Most of these patients took medications immediately before going to bed. (See Dosage and Administration).

Skin: Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above (see Warnings).

Renal toxicity: Rise in BUN has been reported and is apparently dose related. (See Warnings).

Hypersensitivity reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, and exacerbation of systemic lupus erythematosus.

Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving tetracyclines. These conditions disappeared when the drug was discontinued.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported with tetracyclines.

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function are known to occur.

DOSAGE AND ADMINISTRATION. THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF DOXYCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Adults: The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg/day. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

For children above eight years of age: The recommended dosage schedule for children weighing 100 pounds or less is 2 mg/lb of body weight divided into two doses on the first day of treatment, followed by 1 mg/lb of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to 2 mg/lb of body weight may be used. For children over 100 pounds, the usual adult dose should be used.

Uncomplicated gonococcal infections in adults (except anorectal infections in men): 100 mg, by mouth, twice-a-day for 7 days. As an alternate single visit dose, administer 300 mg stat followed in one hour by a second 300 mg dose. The dose may be administered with food, including milk or carbonated beverage, as required.

Acute epididymo-orchitis caused by *N. gonorrhoeae:* 100 mg, by mouth, twice-a-day for at least 10 days.

Primary and secondary syphilis: 300 mg a day in divided doses for at least 10 days.

Uncomplicated urethral, endocervical, or rectal infection in adults caused by *Chlamydia trachomatis:* 100 mg by mouth, twice-a-day for at least 7 days.

Nongonococcal urethritis caused by *C. trachomatis* and *U. urealyticum:* 100 mg, by mouth, twice-a-day for at least 7 days.

Acute epididymo-orchitis caused by *C. trachomatis:* 100 mg, by mouth, twice-a-day for at least 10 days.

The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

When used in streptococcal infections, therapy should be continued for 10 days.

Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration (see Adverse Reactions).

If gastric irritation occurs, it is recommended that doxycycline be given with food or milk. The absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk.

Concomitant therapy: Antacids containing aluminum, calcium or magnesium, sodium bicarbonate, and iron-containing preparations should not be given to patients taking oral tetracyclines.

Studies to date have indicated that administration of doxycycline at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Caution—Federal law prohibits dispensing without prescription.

References **1.** Data on file, Medical Affairs Dept, Parke-Davis. **2.** Segreti J, Trenholme GM: Antibiotics I: Beta-lactam antibiotics, the tetracyclines, chloramphenicol, erythromycin, clindamycin, metronidazole, and the quinolones. *Clin Chest Med* 1986;7:393-412. **3.** Cunha BA, Sibley CM, Ristuccia AM: Review: Doxycycline. *Ther Drug Monit* 1982;4:115-135. **4.** Doryx® (coated doxycycline hyclate pellets) official package insert.

Manufactured by
Faulding International
129 Dew Street,
Thebarton, South Australia, 5031

0838G021

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PARKE-DAVIS
Division of Warner-Lambert Company
Morris Plains, New Jersey 07950

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ANNOUNCEMENT AND CALL FOR PAPERS
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FOR THE AMERICAS, SPAIN, AND PORTUGAL

"THE CHALLENGE OF QUALITY"

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  b) describe methods used, if pertinent
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  d) state conclusions reached
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TRUST

It's never been more important to specify 'Dyazide'.* Because that's the only way you can be sure your patients will receive 'Dyazide' quality...the quality that physicians and their patients have trusted for 25 years.

'Dyazide'—prescribe it with confidence, prescribe it by name. Specify, "Dispense as Written." Ask your patients to make sure that's what they receive when they present your prescription.

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DYAZIDE®
25 mg Hydrochlorothiazide/50 mg Triamterene/SKF

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It's never been more important.

The unique red and white Dyazide® capsule:
Your assurance of SK&F quality.

a product of
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IN UTI

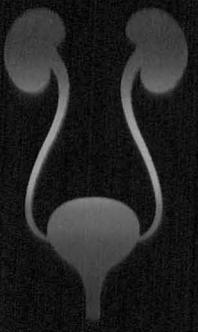
WHAT YOU NEED

A PROVEN HIGH DEGREE OF EFFICACY
BROAD UTI SPECTRUM

For a Brief Summary of Prescribing Information, please see the last page of this advertisement.

WHERE YOU NEED IT

High concentrations in the urinary tract
exceed the MIC_{90} of most uropathogens by 100-fold



NOROXIN® (Norfloxacin, MSD) is contraindicated in patients with a history of hypersensitivity to norfloxacin or the quinolone group of antibacterial agents (e.g., nalidixic acid and cinoxacin).

Norfloxacin should not be used in children or pregnant women.

Patients should be advised to take NOROXIN one hour before or two hours after a meal. Patients should also be advised to drink fluids liberally and not to take antacids concomitantly or within two hours after dosing.

For a Brief Summary of Prescribing Information, please see the last page of this advertisement.

FOR MANY UTI PATIENTS

ALL YOU NEED

TABLETS

NOROXIN®

(NORFLOXACIN | MSD)

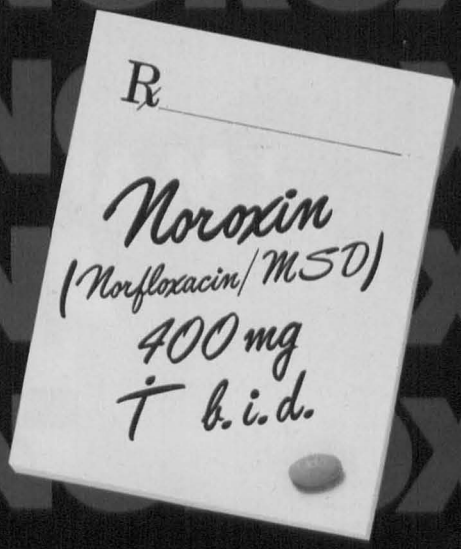
THE UTI SPECIALIST

- Highly effective in clinical trials: 95% cured or improved*
- High degree of aerobe specificity
- Broader UTI spectrum than many oral and parenteral agents
- Generally well tolerated; convenient b.i.d. dosage

*88% cured, 7% improved
Cured: elimination of clinical signs, symptoms, and infecting organism(s).
Improved: eradication of infecting organism(s) with decrease in clinical signs and symptoms.

WHAT YOU NEED WHERE YOU NEED IT ALL YOU NEED FOR MANY UTI PATIENTS

NOROXIN®
(NORFLOXACIN | MSD)
THE UTI SPECIALIST



NOROXIN®
(NORFLOXACIN | MSD)

DESCRIPTION: NOROXIN® (Norfloxacin, MSD) is a synthetic, broad-spectrum antibacterial agent for oral administration. Norfloxacin, a fluoroquinolone, is 1-ethyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid and differs from quinolones by having a fluorine atom at the 6 position and a piperazine moiety at the 7 position.

INDICATIONS AND USAGE: NOROXIN is indicated for the treatment of adults with complicated and uncomplicated urinary tract infections that are caused by susceptible strains of the designated microorganisms listed below:

Escherichia coli; Klebsiella pneumoniae; Enterobacter cloacae; Proteus mirabilis;* indole positive *Proteus* species* (which may include the organisms now called *Proteus vulgaris*, Providencia rettgeri**, and *Morganella morganii*); Pseudomonas aeruginosa; Citrobacter freundii*; Staphylococcus aureus*, Staphylococcus epidermidis*;* and group D streptococci.

Note: Specimens for culture and susceptibility testing should be obtained prior to and during treatment if clinical response warrants. However, NOROXIN may be used to initiate therapy in urinary tract infections prior to the availability of laboratory results.

CONTRAINDICATIONS: NOROXIN is contraindicated in patients with a history of hypersensitivity to norfloxacin or the quinolone group of antibacterial agents (e.g., nalidixic acid and cinoxacin).

WARNINGS: Norfloxacin should not be used in children or pregnant women.

The oral administration of single doses of norfloxacin, 6 times the recommended human clinical dose, caused lameness in immature dogs. Histologic examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs (e.g., nalidixic acid and cinoxacin) also produced erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

PRECAUTIONS: Needle shaped crystals were found in the urine of some volunteers who received either placebo, 800 mg norfloxacin, or 1600 mg norfloxacin (at or twice the recommended daily dose, respectively) while participating in a double-blind, crossover study comparing single doses of norfloxacin with placebo. While crystalluria is not expected to occur under usual conditions with a dosage regimen of 400 mg b.i.d., as a precaution, the daily recommended dosage should not be exceeded and the patient should drink sufficient fluids to ensure a proper state of hydration and adequate urinary output.

Alteration in dosage regimen is necessary for patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Convulsions have been reported rarely with norfloxacin although no causal relationship has been established. Convulsions, increased intracranial pressure, and toxic psychoses have been reported with other drugs in this class. If these reactions occur in patients receiving norfloxacin, the drug should be discontinued and appropriate measures instituted.

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Until more information becomes available, quinolones should be used with caution in patients with known factors which predispose to seizures.

Drug Interactions: Diminished urinary excretion of norfloxacin has been reported during the concomitant administration of probenecid and norfloxacin.

The concomitant use of nitrofurantoin is not recommended since nitrofurantoin may antagonize the antibacterial effect of NOROXIN® (Norfloxacin, MSD) in the urinary tract.

The concomitant administration of norfloxacin with antacids is not recommended.

Information for Patients: Patients should be advised to take NOROXIN one hour before or two hours after a meal. Patients should also be advised to drink fluids liberally and not to take antacids concomitantly or within two hours after dosing.

NOROXIN may cause dizziness or lightheadedness; therefore, patients should know how they react to norfloxacin before they operate an automobile or machinery or engage in activities requiring mental alertness and coordination.

Pregnancy: Pregnancy Category C: Norfloxacin has been shown to produce embryonic loss in monkeys when given in doses 10 times the maximum human dose (400 mg b.i.d.), with peak plasma levels that are 2 to 3 times those obtained in humans. There has been no evidence of a teratogenic effect in any of the animal species tested (rat, rabbit, mouse, monkey) at 6–50 times the human dose. There were no adequate and well controlled studies in pregnant women. Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnant women (see WARNINGS).

Nursing Mothers: It is not known whether norfloxacin is excreted in human milk.

When a 200 mg dose of NOROXIN was administered to nursing mothers, norfloxacin was not detected in human milk. However, because the dose studied was low, because other drugs in this class are secreted in human milk, and because of the potential for serious adverse reactions from norfloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Norfloxacin should not be used in children because it causes arthropathy in juvenile animals (see WARNINGS).

ADVERSE REACTIONS: In clinical trials, NOROXIN was generally well tolerated.

The incidence of subjects reporting drug related adverse experiences in clinical trials involving 1127 subjects was 3.4%. However, the incidence figures below were calculated without reference to drug relationship.

The most common adverse experiences (1%–3%) were either gastrointestinal or neurological: nausea 2.8%, headache 2.7%, and dizziness 1.8%.

Additional reactions (0.3%–1%) were: fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, constipation, flatulence, and heartburn.

Less frequent reactions included: dry mouth, diarrhea, fever, vomiting, and erythema.

CNS effects characterized as generalized seizures and myoclonus have been reported rarely with NOROXIN. A causal relationship to NOROXIN has not been established (see PRECAUTIONS). Visual disturbances have been reported with drugs in this class.

Abnormal laboratory values observed in these 1127 subjects in clinical trials were eosinophilia 1.8%, elevation of ALT (SGPT) and AST (SGOT) 1.8%, increased alkaline phosphatase 1.4%, and decreased WBC or neutrophil count 1.2%. Those occurring less frequently included increased BUN, serum creatinine, and LDH, and decreased hematocrit.

The following additional adverse reactions have been reported since the drug was marketed:

Hypersensitivity Reactions: Hypersensitivity reactions have been reported including anaphylactoid reactions, angioedema, urticaria, arthritis, arthralgia, and myalgia.

Skin: Toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, photosensitivity.

Gastrointestinal: Pseudomembranous colitis.

Nervous System/Psychiatric: Psychic disturbances including psychotic reactions and confusion, paresthesia.

Hematologic: Neutropenia, leukopenia, thrombocytopenia.

DOSAGE AND ADMINISTRATION: NOROXIN® (Norfloxacin, MSD) should be taken one hour before or two hours after a meal with a glass of water. Patients receiving NOROXIN should be well hydrated (see PRECAUTIONS).

Normal Renal Function: The recommended dosage of NOROXIN is: Uncomplicated urinary tract infections: 400 mg twice daily for 7 to 10 days. Complicated urinary tract infections: 400 mg twice daily for 10 to 21 days. Maximum total daily dosage should not exceed 800 mg per day.

Renal Impairment: NOROXIN may be used for the treatment of urinary tract infections in patients with renal insufficiency. In patients with a creatinine clearance rate of 30 mL/min/1.73m^2 or less, the recommended dosage is one 400 mg tablet once daily for the duration given above. At this dosage, the urinary concentration exceeds the MICs for most urinary pathogens susceptible to norfloxacin, even when the creatinine clearance is less than 10 mL/min/1.73m^2.

When only the serum creatinine level is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Males: $= \dfrac{(\text{weight in kg}) \times (140 - \text{age})}{(72) \times \text{serum creatinine (mg/100 mL)}}$

Females: $= (0.85) \times$ (above value)

Elderly: Elderly patients with a creatinine clearance of greater than 30 mL/min/1.73m^2 should receive the dosages recommended under *Normal Renal Function*.

Elderly patients with a creatinine clearance of 30 mL/min/1.73m^2 or less should receive 400 mg once daily as recommended under *Renal Impairment*.

HOW SUPPLIED: Dark pink, oval shaped, film-coated tablets, coded MSD 705 on one side and NOROXIN on the other, in bottles of 100, unit-of-use bottles of 20, and unit-dose packages of 100.

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

J8N025R(408)

MSD
MERCK SHARP & DOHME

Hypertension control that doesn't disturb the delicate balance of the individual.

*ONCE DAILY**

ISOPTIN® SR

(verapamil HCl) 240 mg

Sustained-Release Tablets

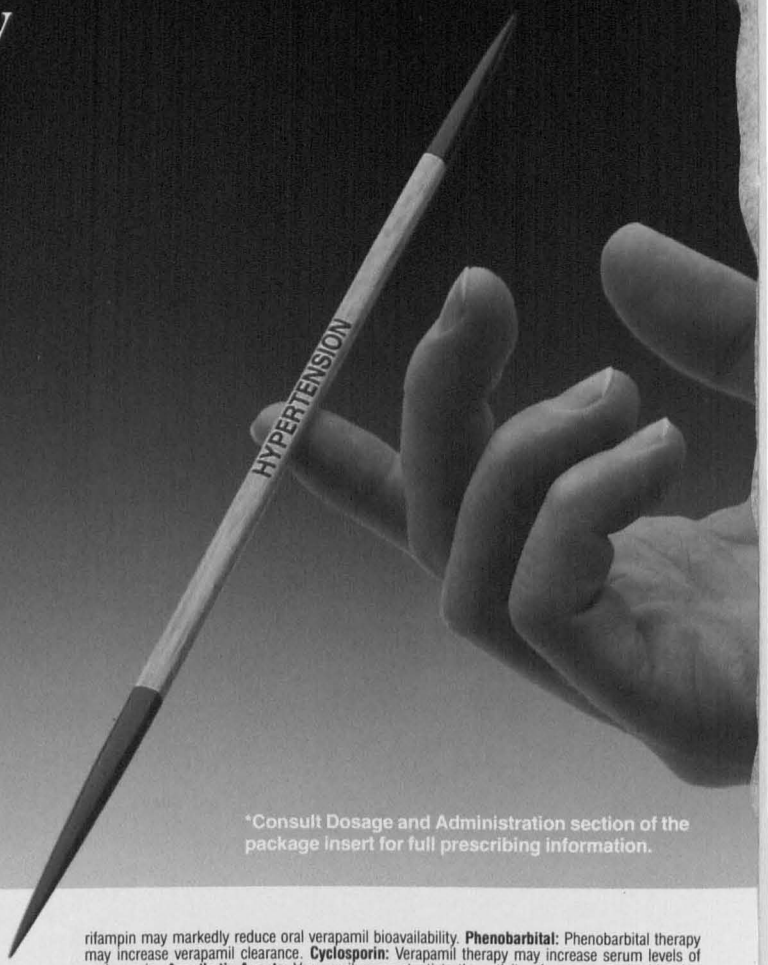
Effective monotherapy that respects the individual profiles of more patient types.[1,2]

*Consult Dosage and Administration section of the package insert for full prescribing information.

Please see brief summary on reverse side for safety information.

First line anti-hypertensive therapy for more patient types.

- Low incidence of fatigue.
- Low incidence of depression.
- Impotence rarely reported.
- No changes seen in the renin-angiotensin-aldosterone system.[3,4]
- Particularly effective in patients with low renin levels.[5]
- No adverse effect on serum potassium, uric acid or blood glucose levels.[5,6]
- Does not increase serum cholesterol or triglycerides.[5,7]



*ONCE DAILY**

ISOPTIN® SR

(verapamil HCl) 240mg

Sustained-Release Tablets

*Consult Dosage and Administration section of the package insert for full prescribing information.

CONTRAINDICATIONS: 1) Severe left ventricular dysfunction (see WARNINGS). 2) Hypotension (less than 90 mmHg systolic pressure) or cardiogenic shock. 3) Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker). 4) 2nd or 3rd degree AV block (except in patients with a functioning artificial ventricular pacemaker). 5) Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g., Wolff-Parkinson-White, Lown-Ganong-Levine syndromes). 6) Patients with known hypersensitivity to verapamil hydrochloride.

WARNINGS: Heart Failure: ISOPTIN should be avoided in patients with severe left ventricular dysfunction. Patients with milder ventricular dysfunction should, if possible, be controlled before verapamil treatment. ISOPTIN should be avoided in patients with any degree of left ventricular dysfunction if they are receiving a beta adrenergic blocker (see DRUG INTERACTIONS). **Hypotension:** ISOPTIN (verapamil HCl) may produce occasional symptomatic hypotension. **Elevated Liver Enzymes:** Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent. **Accessory Bypass Tract (Wolff-Parkinson-White):** Patients with paroxysmal and/or chronic atrial flutter or atrial fibrillation and a coexisting accessory AV pathway may develop increased antegrade conduction across the accessory pathway producing a very rapid ventricular response or ventricular fibrillation after receiving intravenous verapamil. While this has not been reported with oral verapamil, it should be considered a potential risk (see Contraindications). Treatment is usually D.C.-cardioversion. **Atrioventricular Block:** The effect of verapamil on AV conduction and the SA node may cause asymptomatic 1st degree AV block and transient bradycardia. Higher degrees of AV block, while infrequent (0.8%), may require a reduction in dosage or, in rare instances, discontinuation of verapamil HCl. **Patients with Hypertrophic Cardiomyopathy (IHSS):** Although verapamil has been used in the therapy of patients with IHSS, severe cardiovascular decompensation and death have been noted in this patient population.

PRECAUTIONS: Impaired Hepatic or Renal Function: Verapamil is highly metabolized by the liver with about 70% of an administered dose excreted as metabolites in the urine. In patients with impaired hepatic function the dose should be cut to 30% of the usual dose and the patient closely monitored. In patients with impaired renal function verapamil should be administered cautiously and the patients monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacological effects (see Overdose). **Use in Patients with Attenuated (Decreased) Neuromuscular Transmission:** Verapamil decreases neuromuscular transmission and may prolong recovery from neuromuscular blocking agents. In patients with attenuated neuromuscular transmission lower doses of verapamil may be warranted.

Drug Interactions: Beta Blockers: Concomitant use of ISOPTIN and oral beta-adrenergic blocking agents may result in additive negative effects on heart rate, atrioventricular conduction, and/or cardiac contractility. Excessive bradycardia and AV block, has been reported. The combination should be used only with caution and close monitoring. **Digitalis:** Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated. However, chronic verapamil treatment increases serum digoxin levels by 50% to 75% during the first week of therapy and this can result in digitalis toxicity. Upon discontinuation of ISOPTIN (verapamil HCl), the patient should be reassessed to avoid underdigitalization. **Antihypertensive Agents:** Verapamil administered concomitantly with oral antihypertensive agents (e.g., vasodilators, angiotensin-converting enzyme inhibitors, diuretics, alpha and beta adrenergic blockers) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored. **Antiarrhythmic Agents: Disopyramide:** Disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration. **Flecainide:** Concomitant administration of flecainide and verapamil may result in additive negative inotropic effect and prolongation of atrioventricular conduction. **Quinidine:** In patients with hypertrophic cardiomyopathy (IHSS), concomitant use of verapamil and quinidine may result in significant hypotension. **Other: Nitrates:** The pharmacologic profile of verapamil and nitrates as well as clinical experience suggest beneficial interactions. **Cimetidine:** Variable results on clearance have been obtained in acute studies of healthy volunteers; clearance of verapamil was either reduced or unchanged. **Lithium:** Pharmacokinetic (lowering of serum lithium levels) and pharmacodynamic (increased sensitivity to the effects of lithium) interactions between oral verapamil and lithium have been reported. **Carbamazepine:** Verapamil therapy may increase carbamazepine concentrations and produce related side effects during combined therapy. **Rifampin:** Therapy with rifampin may markedly reduce oral verapamil bioavailability. **Phenobarbital:** Phenobarbital therapy may increase verapamil clearance. **Cyclosporin:** Verapamil therapy may increase serum levels of cyclosporin. **Anesthetic Agents:** Verapamil may potentiate the activity of neuromuscular blocking agents and inhalation anesthetics. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** There was no evidence of a carcinogenic potential of verapamil administered to rats for two years. Verapamil was not mutagenic in the Ames test. Studies in female rats did not show impaired fertility. Effects on male fertility have not been determined. **Pregnancy (Category C):** There are no adequate and well-controlled studies in pregnant women. ISOPTIN crosses the placental barrier and can be detected in umbilical vein blood at delivery. This drug should be used during pregnancy, labor, and delivery, only if clearly needed. **Nursing Mothers:** ISOPTIN is excreted in human milk, therefore, nursing should be discontinued while verapamil is administered. **Pediatric Use:** Safety and efficacy of ISOPTIN in children below the age of 18 years have not been established.

ADVERSE REACTIONS: Constipation 7.3%, dizziness 3.3%, nausea 2.7%, hypotension 2.5%, headache 2.2%, edema 1.9%, CHF/pulmonary edema 1.8%, fatigue 1.7%, dyspnea 1.4%, bradycardia 1.4%, 2° and 3° AV block 0.8%, rash 1.2%, flushing 0.6% and elevated liver enzymes (see WARNING). The following reactions, reported in less than 1.0% of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain; they are mentioned to alert the physician to a possible relationship: angina pectoris, atrioventricular dissociation, arthralgia and rash, blurred vision, cerebrovascular accident, chest pain, claudication, confusion, diarrhea, dry mouth, ecchymosis or bruising, equilibrium disorders, erythema multiforme, exanthema, gastrointestinal distress, gingival hyperplasia, gynecomastia, hair loss, hyperkeratosis, impotence, increased urination, insomnia, macules, muscle cramps, myocardial infarction, palpitations, paresthesia, psychotic symptoms, purpura (vasculitis), shakiness, somnolence, spotty menstruation, Steven-Johnson syndrome, sweating, syncope, urticaria.

Treatment of Acute Cardiovascular Adverse Reactions: Whenever severe hypotension or complete AV block occur following oral administration of verapamil, the appropriate emergency measures should be applied immediately, e.g., intravenously administered isoproterenol HCl, levarterenol bitartrate, atropine (all in the usual doses), or calcium gluconate (10% solution). If further support is necessary, inotropic agents (dopamine or dobutamine) may be administered. Actual treatment and dosage should depend on the severity and the clinical situation and the judgment and experience of the treating physician.

OVERDOSAGE: Treatment of overdosage should be supportive. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase calcium ion flux across the slow channel, and have been used effectively in treatment of deliberate overdosage with verapamil. Clinically significant hypotensive reactions or fixed high degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including cardiopulmonary resuscitation.

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REFERENCES: 1. Speders S, et al, Efficacy and Safety of verapamil SR 240 mg in Essential Hypertension: Results of a Multicenter Phase IV study. *J. Cardiovasc Pharmacol* 1989: 13 (Suppl 4); S47-S49. 2: Cubeddu LX, Aranda J, Singh B, et al: *JAMA* 1986; 256:2214-2221. 3. Schmieder RE, Messerli FH, Garavaglia GE, et al: *Circulation* 1987:75:1030-1036. 4. Leonetti G, Cuspidi C, Sampieri L, et al: *J Cardiovasc Pharmacol* 1982; 4:S325-S329. 5. Stroh JA, Frishman WH. verapamil in the treatment of essential hypertension: *CV&R* 1987 (Aug): 32-39. 6. Leonetti G, Pasotti C, Ferrari GP, et al: *Acta Medica Scand* 1984: (Suppl) 681-137-141. 7. Lewis GRJ, Stewart DJ, Lewis BM, The antihypertensive effect of oral verapamil. *Excerpta Medica*, 1981 P. 273

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

BASF Group

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2719/6-89

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What's a common denominator of most heart attack victims?

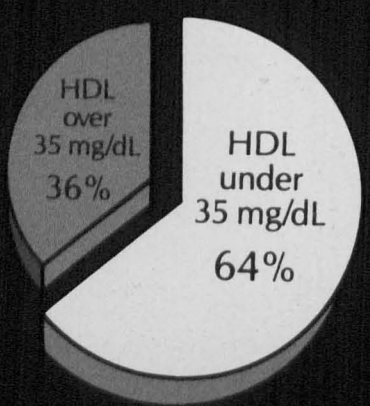
HDL

<35

mg/dL

Mixed hyperlipidemias—elevated cholesterol *and* triglycerides—are common among heart attack victims,[1] 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.[2]

HEART ATTACK PATIENTS
(PROCAM TRIAL)[2]



PARKE-DAVIS

A powerful case for

LOPID®

BID

(gemfibrozil) 600-mg Tablets

Raised low HDL 25%

—in patients whose baseline HDL was below 35 mg/dL in the landmark Helsinki Heart Study (HHS).[3]

Reduced heart attack incidence* up to 62%

—in these HHS patients and 45% in HHS patients whose baseline HDL was below the median (46.4 mg/dL). Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).[3]

Raised HDL levels 1½ to 3 times more effectively than lovastatin

—in a 12-week, double-blind, randomized trial among patients with moderate to severe hyperlipidemia. Lovastatin achieved greater reductions in total serum cholesterol than gemfibrozil in this study population.[4]

RAISES HDL DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of coronary heart disease (CHD) 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.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, 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 Münster Trial.* Zürich: Panscientia Verlag; 1986:8-9. **3.** Data on file, Medical Affairs Dept, Parke-Davis **4.** Tikkanen MJ, Helve E, Jäättelä A, et al. Comparison between lovastatin and gemfibrozil in the treatment of primary hypercholesterolemia: the Finnish Multicenter Study. *Am J Cardiol.* 1988;62:35J-43J.

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 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 overdosage, 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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Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

0737G013

PD-56-JA-5860-P-1(10-89)

Contraindications: PRINIVIL® (Lisinopril, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Warnings: *Angioedema:* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including PRINIVIL. In such cases, PRINIVIL should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered** (see ADVERSE REACTIONS).

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of the use of PRINIVIL in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis (see PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS). In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first 2 weeks of treatment and whenever the dose of PRINIVIL and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Neutropenia/Agranulocytosis: Another ACE inhibitor has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of PRINIVIL are insufficient to show that PRINIVIL does not cause agranulocytosis at similar rates. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including PRINIVIL, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another ACE inhibitor suggests that these increases are usually reversible upon discontinuation of PRINIVIL and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when PRINIVIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of PRINIVIL and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia: In clinical trials, hyperkalemia (serum potassium >5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.0% of patients with congestive heart failure. In most cases, these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with PRINIVIL (see *Drug Interactions*).

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, PRINIVIL may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur, especially following the first dose of PRINIVIL. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with PRINIVIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with PRINIVIL. The possibility of hypotensive effects with PRINIVIL can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with PRINIVIL. If it is necessary to continue the diuretic, initiate therapy with PRINIVIL at a dose of 5 mg daily, and provide close medical supervision after the initial dose for at least 2 hours and until blood pressure has stabilized for at least an additional hour (see WARNINGS and DOSAGE AND ADMINISTRATION). When a diuretic is added to the therapy of a patient receiving PRINIVIL, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic (see DOSAGE AND ADMINISTRATION).

Indomethacin: In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of PRINIVIL alone were compared to PRINIVIL given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant.

Other Agents: PRINIVIL has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No clinically important pharmacokinetic interactions occurred when PRINIVIL was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of PRINIVIL.

Agents Increasing Serum Potassium: PRINIVIL attenuates potassium loss caused by thiazide-type diuretics. Use of PRINIVIL with potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was usually reversible upon discontinuation of lithium and the ACE inhibitor. It is recommended that serum lithium levels be monitored frequently if PRINIVIL is administered concomitantly with lithium.

Pregnancy Category C: Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline-supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to ACE inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man. Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorptions at an oral dose of lisinopril of 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). A single intravenous dose of 15 mg/kg of lisinopril administered to pregnant rabbits on gestation days 16, 21, or 26 resulted in 88% to 100% fetal death.

There are no adequate and well-controlled studies of lisinopril in pregnant women. However, data are available that show drugs of this class cross the human placenta. Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined, PRINIVIL® (Lisinopril, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity.

Nursing Mothers: It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when PRINIVIL is given to a nursing mother.

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

Adverse Reactions: PRINIVIL has been found to be generally well tolerated in controlled clinical trials involving 2,003 patients and subjects.

The most frequent clinical adverse experiences in controlled trials with monotherapy with PRINIVIL were: dizziness (6.3%), headache (5.3%), fatigue (3.3%), diarrhea (3.2%), upper respiratory symptoms (3.0%), and cough (2.9%), all of which were more frequent than in placebo-treated patients. For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6% of patients. In clinical trials, the overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range.

Other adverse experiences occurring in greater than 1% of patients and subjects treated with monotherapy with PRINIVIL in controlled clinical trials were: nausea (2.3%), hypotension (1.8%), rash (1.5%), orthostatic effects (1.4%), asthenia (1.3%), chest pain (1.3%), vomiting (1.3%), and dyspnea (1.1%). For information on adverse experiences occurring in greater than 1% of patients and subjects treated with PRINIVIL plus hydrochlorothiazide in controlled clinical trials, see Prescribing Information.

Clinical adverse experiences occurring in 0.3% to 1% of patients treated with monotherapy with PRINIVIL in the controlled trials and rarer, serious, possibly drug-related events reported in uncontrolled studies or marketing experience included: *Body as a Whole:* Chest discomfort, fever, flushing. *Cardiovascular:* Angina pectoris, orthostatic hypotension, rhythm disturbances, tachycardia, peripheral edema, palpitation. *Digestive:* Abdominal pain, anorexia, constipation, flatulence. *Metabolism:* Gout. *Musculoskeletal:* Joint pain, shoulder pain. *Nervous System/Psychiatric:* Depression, somnolence, insomnia, stroke. *Respiratory System:* Bronchitis, sinusitis, pharyngeal pain. *Urogenital:* Oliguria, progressive azotemia, acute renal failure. *Other:* Blurred vision, pruritus, urinary tract infection, vasculitis. *Angioedema:* Angioedema has been reported in patients receiving PRINIVIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with PRINIVIL should be discontinued and appropriate therapy instituted immediately (see WARNINGS). *Hypotension:* In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.5% of hypertensive patients (see WARNINGS). In patients with congestive heart failure, hypotension occurred in 5% and syncope occurred in 1% of patients. These adverse experiences were cause for discontinuation of therapy in 1.3% of these patients.

Clinical Laboratory Test Findings:

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS).

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2% of patients with essential hypertension treated with PRINIVIL alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis (see PRECAUTIONS). Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 9.1% of patients with congestive heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g % and 1.3 vol %, respectively) occurred frequently in patients treated with PRINIVIL but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Overall, 2.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%), and serum potassium (0.4%).

Dosage and Administration: *Initial Therapy:* In patients with uncomplicated essential hypertension not on diuretic therapy, the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20 to 40 mg per day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. Doses up to 80 mg have been used but do not appear to give a greater effect. If blood pressure is not controlled with PRINIVIL alone, a low dose of a diuretic may be added. Hydrochlorothiazide (12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of PRINIVIL.

Diuretic-Treated Patients: In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of PRINIVIL. The diuretic should be discontinued, if possible, for 2 to 3 days before beginning therapy with PRINIVIL to reduce the likelihood of hypotension (see WARNINGS). The dosage of PRINIVIL should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with PRINIVIL alone, diuretic therapy may be resumed as described above.

If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least 2 hours and until blood pressure has stabilized for at least an additional hour (see WARNINGS and PRECAUTIONS, *Drug Interactions*).

Concomitant administration of PRINIVIL with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Use in Elderly: In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of PRINIVIL. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution.

Dosage Adjustment in Renal Impairment: The usual dose of PRINIVIL (10 mg) is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≥ 10 mL/min and ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 5 mg once daily. For patients with creatinine clearance < 10 mL/min (usually on hemodialysis), the recommended initial dose is 2.5 mg. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

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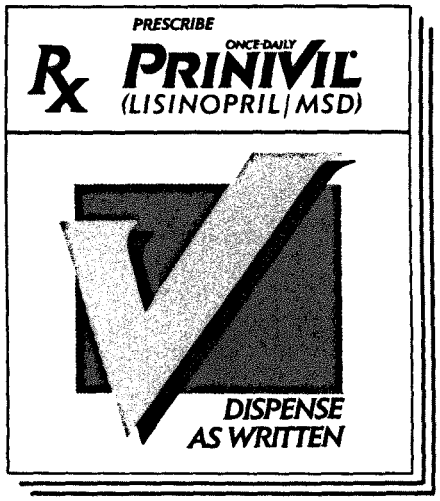

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