Drug effects on laboratory values

JOHN R. ZOND, DO

An abnormal laboratory value in any patient must be explained. Three factors may alter the laboratory test results: diet, disease, and drugs. Perusal of the *Physicians' Desk Reference* reveals the enormous influence drugs can have on the laboratory test results. The prescribing physician should be aware of any potential side effects of a drug he or she is prescribing and enlist the assistance of a qualified pathologist to decide what effects, if any, the medication has on observed anomalies. The clinical pathologist can also help the clinician to decide what further steps need to be taken to elucidate the problem.

(Key words: Laboratory tests, drugs)

Clinicians confronted by an abnormal laboratory test result have the choice of chalking the result up to laboratory error or evaluating the cause of the anomaly. Generally, "three Ds"—diet, disease, drugs—can cause abnormal laboratory results. On receipt of a patient's test results, the clinician must decide if any, some, or all of these variables are causing the abnormality.

When prescribing any medication, the physician should be aware of possible iatrogenic laboratory test alterations and entertain the possibility that a disease process or change in dietary habits may be causing the abnormality until such a possibility is ruled out.

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Examination of the effects of all medicines in the pharmacopoeia is beyond the scope of this article. Therefore, the focus will be on some of the medications encountered in primary care. The general drug classifications to be considered herein are as follows: (1) antihypertensive and cardiac medications; (2) psychotherapeutic agents; (3) nonsteroidal anti-inflammatory drugs (NSAIDs); (4) androgen and anabolic steroids; (5) antiulcer medications; (6) antiseizure medications; (7) antibiotics; (8) antihistamines; and (9) vitamins.

Antihypertensive and cardiac medications

The effects of antihypertensive and cardiac medications are given in *Table 1*. Atenolol has been shown to increase liver enzyme and bilirubin levels. Betaxolol, a compound with similar action, has been reported to increase the liver enzymes, decrease serum potassium levels, increase serum glucose levels, and increase triglyceride and low-density lipoprotein cholesterol (LDL-C) levels, an undesirable side effect encountered with some cardiac medication. Labetalol hydrochloride, the last member of this subgroup, also increases liver enzyme levels but has no appreciable effect on other laboratory values.

Captopril, an angiotensin-converting enzyme (ACE) inhibitor, also increases liver enzymes, as well as bilirubin, blood urea nitrogen (BUN), creatinine, and serum high-density lipoprotein cholesterol (HDL-C) levels. Lisinopril, another ACE inhibitor, also increases liver enzymes, as well as bilirubin, BUN, creatinine, and potassium levels. Enalapril maleate, the third ACE inhibitor to be considered, increases liver enzymes, as well as bilirubin, BUN, creatinine, and sodium levels.

Calcium channel blockers seem to have the same profile as the ACE inhibitors. Diltiazem has been shown to increase liver, lactate dehydrogenase (LDH), and creatine phosphokinase (CPK) enzyme levels, as well as bilirubin and glucose levels. Nicardipine hydrochloride is a relatively innocuous calcium channel blocker, in that it only tends to increase liver enzyme levels. Nifedipine, in contrast, tends to increase liver, LDH, and CPK enzyme levels, as well as BUN.

Prazosin hydrochloride, an α-blocker, has no known effects on liver enzymes; however, it does decrease serum LDH levels, making it an unwise choice for a patient with high serum lipid levels.

Furosemide, a diuretic, increases serum BUN, LDH, and triglyceride levels, and decreases potassium and calcium levels. Hydrochlorothiazide, another diuretic, has been shown to increase serum BUN, creatinine, potassium, LDL-C, and triglyceride levels.

Psychotherapeutic agents

The drugs discussed in this section appear in *Table 2*.

Chlordiazepoxide hydrochloride and diazepam, two benzodiazepines used as anxiolytics, both have been shown to increase liver enzyme levels and cause neutropenia. Doxepin (with or without hydrochloride), one of the tricyclic antidepressants, has no effect on liver enzymes, but has been shown to cause leukopenia and thrombocytopenia. Fluoxetine hydrochloride has been shown to increase serum liver enzymes and to decrease serum sodium levels. Nortriptyline hydrochloride, another tricyclic antidepressant, can increase liver enzyme levels and cause neutropenia or thrombocytopenia (or both). Trazodone hydrochloride, an antidepressant, tends to increase serum liver enzyme levels and cause leukopenia or neutropenia (or both). Haloperidol, an antipsychotic, can cause a decrease in serum sodium, as well as leukopenia and erythropenia.

NSAIDs

The effects of the NSAIDs are given in *Table 3*. Flurbiprofen has been shown to increase liver enzyme as well as BUN and creatinine levels, and can prolong bleeding time and cause decreased platelet aggregation. Ibuprofen, the most popular NSAID, has been shown to increase liver enzyme levels, prolong bleeding time, and inhibit platelet aggregation. Naproxen (with or without sodium) increases serum liver enzymes, prolongs bleeding time, and decreases platelet aggregation. Piroxicam, the last NSAID to be considered here, has been shown to increase liver enzyme as well as serum BUN and creatinine levels.

Hypoglycemic agents

Table 4 shows the effects of the hypoglycemic agents. Both glipizide and glyburide have been shown to increase LDH and liver enzyme levels as well as serum BUN and creatinine levels. These drug also have been shown to increase white blood cell, neutrophil, and platelet counts, and to cause hemolytic or aplastic anemias.

Lipid-lowering agents

Refer to *Table 5* for the effects of lipid-lowering agents.

Gemfibrozil has been shown to increase LDH and liver enzyme levels as well as serum bilirubin levels. It has also been shown to decrease the hematocrit value and hemoglobin, WBC, and platelet levels. Probucol can cause increased liver and CPK enzyme levels, as well as increased serum bilirubin, uric acid, BUN, and glucose levels.

Androgen and anabolic steroids

This class of drugs (*Table 6*) can have a profound effect on serum lipid levels in the unwitting abuser. Testosterone, like other medications in this group, decreases HDL-C and LDL-C levels, red blood cell counts, and thyroid function tests. These medications also increase liver enzyme, BUN, and creatine levels.

Antiulcer agents

Table 7 details the antiulcer agents discussed in this section.

Cimetidine has been shown to increase serum liver enzyme levels as well as serum creatinine levels. It has also been shown to cause

(continued on page 357)

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Please see brief summary of prescribing information on next page.

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BRIEF SUMMARY

CARDIZEM® CD (diltiazem hydrochloride) Capsules

CARDIZEM® SR (diltiazem hydrochloride) Sustained Release Capsules

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

WARNINGS

1. Cardiac Conduction. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

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

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

ADVERSE	DILTIAZEM N=315 # PTS (%)	PLACEBO N=211 # PTS (%)
Headache	38 (12%)	17 (8%)
AV Block First Degree	24 (7.6%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG Abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.6%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	—
Alk Phos Increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Insomnia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV Block Second Degree	2 (0.6%)	—

The following table presents the most common adverse reactions reported in placebo-controlled trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

ADVERSE REACTION	CARDIZEM CD N=324	PLACEBO N=175
HEADACHE	9.0%	8.0%
BRADYCARDIA	4.3%	2.3%
EDEMA	3.7%	2.3%
DIZZINESS	3.1%	3.4%
ECG ABNORMALITY	3.1%	2.9%
AV BLOCK FIRST DEGREE	2.2%	—
ASTHENIA	1.9%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM SR Capsules involving over 3000 patients, the most common events (ie, greater than 1%) were edema (4.9%), headache (4.9%), dizziness (3.5%), asthenia (2.7%), first-degree AV block (2.2%), bradycardia (1.6%), flushing (1.5%), nausea (1.4%), rash (1.3%), and dyspepsia (1.2%).

In addition, the following events were reported infrequently (less than 1%).

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

HOW SUPPLIED

CARDIZEM® CD (diltiazem hydrochloride) is available as capsules of 180 mg, 240 mg, and 300 mg in bottles of 30 and 90, and in UDIP® packages of 100.

CARDIZEM® SR (diltiazem hydrochloride) is available as sustained release capsules of 60 mg, 90 mg, and 120 mg in bottles of 100, and in UDIP® packages of 100.

Product Information as of October 1991

References: 1. Data on file, Marion Merrell Dow Inc. 2. Cramer JA, Mattson RH, Prevey ML, et al. JAMA. 1989;261(22):3273-3274.

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Table 1
Antihypertensive and Cardiac Medication Effects on Clinical Laboratory Results

Medication	AST/ SGOT*	ALT/ SGPT	Alk PO_4	LDH	CPK	Bili	BUN	Creat	K	Na	Ca	Glu	HDL-C	LDL-C	Triglycerides
Atenolol	▲	▲	▲			▲									
Betaxolol hydrochloride	▲	▲		▲					▼			▲		▲	▲
Labetalol hydrochloride	▲	▲													
Captopril	▲	▲	▲			▲	▲	▲							
Lisinopril	▲	▲	▲			▲	▲	▲	▲						
Enalapril maleate	▲	▲	▲			▲	▲	▲		▲					
Diltiazem	▲	▲	▲	▲	▲	▲						▲			
Nicardipine hydrochloride	▲	▲	▲												
Nifedipine	▲	▲	▲	▲	▲		▲	▲				▲			
Verapamil	▲	▲	▲												
Prazosin hydrochloride														▼	
Furosemide							▲		▼		▼			▲	▲
Hydrochloro-thiazide							▲	▲	▲					▲	▲

*Key: AST = aspartate aminotransferase, formerly SGOT; SGOT = serum glutamic-oxaloacetic transaminase; ALT = alanine aminotransferase, formerly SGPT; SGPT = serum glutamic-pyruvic transaminase; Alk PO_4 = alkaline phosphatase; LDH = serum lactate dehydrogenase; CPK = creatine kinase; Bili = bilirubin; BUN = blood urea nitrogen; Creat = creatinine; K = potassium; Na = sodium; Ca = calcium; Glu = glucose; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; ▲ = increased; ▼ = decreased.

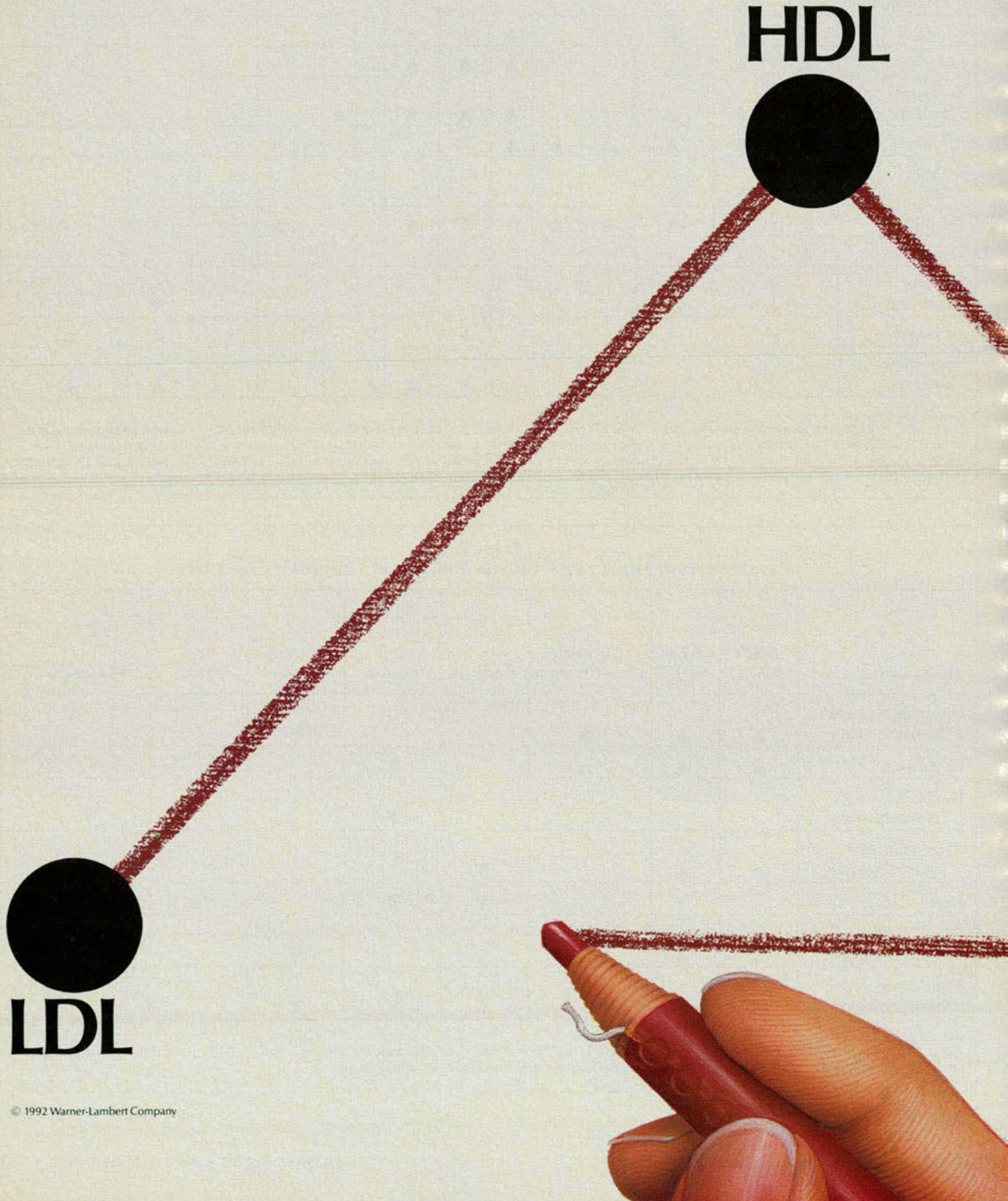
Table 2
Psychotherapeutic Agents' Effects on Clinical Laboratory Results

Medication	AST/ SGOT*	ALT/ SGPT	Alkaline phosphatase	Sodium	White blood cell count	Neutro-phils	Red blood cell count	Platelets
Chlordiazepoxide hydrochloride	▲	▲	▲			▼		
Diazepam	▲	▲	▲		▼			
Doxepin hydrochloride					▼			▼
Fluoxetine hydrochloride	▲	▲		▼				
Haloperidol				▼	▼		▼	
Nortriptyline hydrochloride	▲	▲	▲			▼		▼
Trazodone hydrochloride	▲	▲			▼	▼		

*Key: AST = aspartate aminotransferase, formerly SGOT; SGOT = serum glutamic-oxaloacetic transaminase; ALT = alanine aminotransferase, formerly SGPT; SGPT = serum glutamic-pyruvic transaminase; ▲ = increased; ▼ = decreased.

(continued on page 361)

Make this connection to reduce heart attack risk



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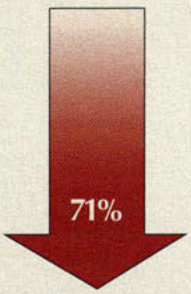
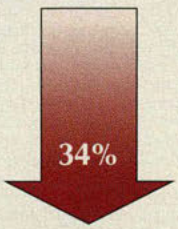
To reduce heart attack risk, don't overlook coexisting low HDL, high triglycerides, and high LDL. A recently published analysis of data from a Helsinki Heart Study subgroup shows why:

LOPID reduced the incidence of heart attack* 71%



—in a high-risk subgroup of patients with multiple lipid disorders. While the overall reduction in heart attack was 34%, the greatest reduction in heart attack was achieved among those LOPID patients with baseline triglycerides >200 mg/dL and baseline LDL/HDL >5 (n = 154).[†1]



LOPID® (gemfibrozil) 600-mg Tablets

BID

TREATS THE ENTIRE TRIAD DRAMATICALLY REDUCES HEART ATTACK

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. LOPID is not indicated for the treatment of patients with low HDL as their only lipid abnormality.

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.

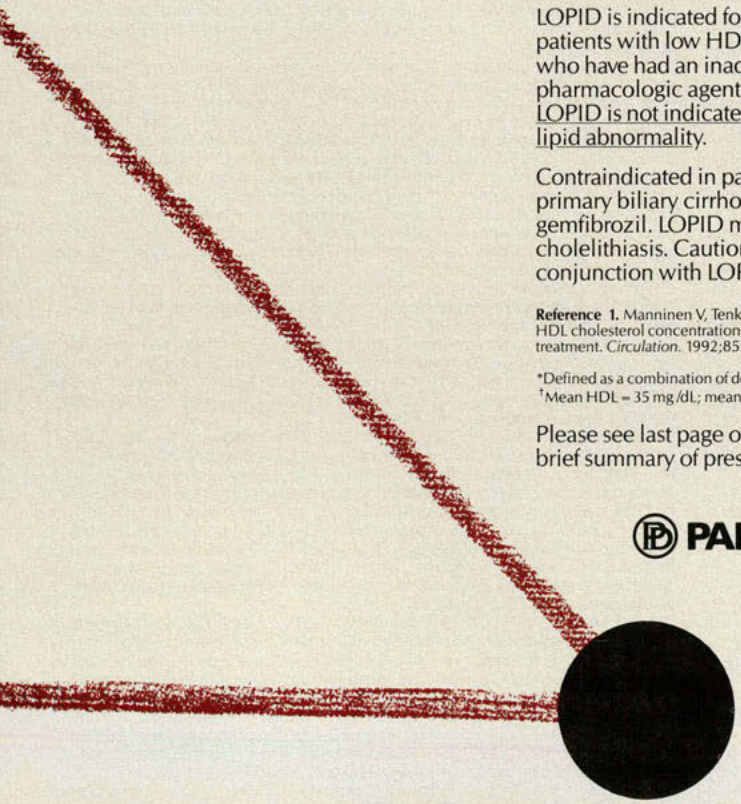
Reference 1. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: implications for treatment. *Circulation*. 1992;85:37-45.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.
†Mean HDL = 35 mg/dL; mean LDL = 208 mg/dL; $P = .005$; 95% CI 21.2 to 118.6.

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

PARKE-DAVIS

BOOTS PHARMACEUTICALS



TRIGLYCERIDES

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

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

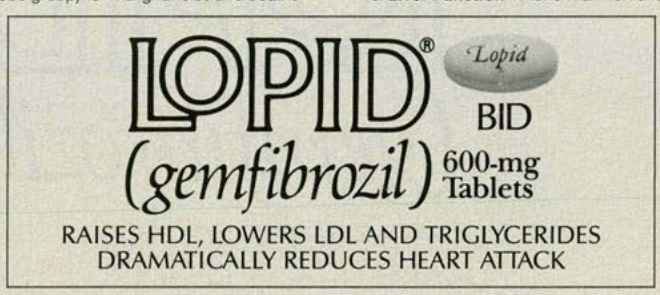
2. Preexisting gallbladder disease (See WARNINGS).

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 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.

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Table 3
NSAIDS Effect on Clinical Laboratory Results

Medication	Test					
	AST/ SGOT*	ALT/ SGPT	BUN	Creatinine	Bleeding time	Platelet aggregation
Flurbiprofen	▲	▲	▲	▲	▲	▼
Ibuprofen	▲	▲			▲	▼
Naproxen	▲	▲			▲	▼
Piroxicam	▲	▲	▲	▲		

*Key: AST = aspartate aminotransferase, formerly SGOT; SGOT = serum glutamic-oxaloacetic transaminase; ALT = alanine aminotransferase, formerly SGPT; SGPT = serum glutamic-pyruvic transaminase; BUN = blood urea nitrogen; ▲ = increased; ▼ = decreased.

Table 4
Hypoglycemic Medication Effects on Clinical Laboratory Results

Medication	Test									Finding	
	AST/ SGOT*	ALT/ SGPT	LDH	Alk PO_4	BUN	Creat	WBC	Neutrophils	Plt	Hemolytic anemia	Aplastic anemia
Glipizide	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲
Glyburide	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲

*Key: AST = aspartate aminotransferase, formerly SGOT; SGOT = serum glutamic-oxaloacetic transaminase; ALT = alanine aminotransferase, formerly SGPT; SGPT = serum glutamic-pyruvic transaminase; LDH = lactate dehydrogenase; Alk PO_4 = alkaline phosphatase; BUN = blood urea nitrogen; Creat = creatinine; WBC = white blood cell count; Plt = platelets; ▲ = increased; ▼ = decreased.

Table 5
Lipid Lowering Medication Effects on Clinical Laboratory Values

Medication	Test												
	AST/ SGOT*	ALT/ SGPT	Alk PO_4	LDH	CPK	Bili	UA	BUN	Glucose	Hgb	Hct	WBC	Plt
Gemfibrozil	▲	▲	▲	▲		▲				▲	▲	▲	▲
Probucol	▲	▲	▲		▲	▲	▲	▲	▲				

*Key: AST = aspartate aminotransferase, formerly SGOT; SGOT = serum glutamic-oxaloacetic transaminase; ALT = alanine aminotransferase, formerly SGPT: SGPT = serum glutamic-pyruvic transaminase; Alk PO_4 = alkaline phosphatase; LDH = lactate dehydrogenase; CPK = creatine kinase; Bili = bilirubin; UA = uric acid; BUN = blood urea nitrogen; Hgb = hemoglobin; Hct = hematocrit; WBC = white blood cell count; Plt = platelets; ▲ = increased; ▼ = decreased.

Table 6
Androgen and Anabolic Steroid Effect on Clinical Laboratory Results

Medication	Tests								
	HDL-C*	LDL-C	RBC count	Thyroid function tests	AST/ SGOT	ALT/ SGPT	Alk PO_4	BUN	Creatinine
Testosterone	▼	▲	▲	▲	▲	▲	▲	▲	▲
Norethandrolone	▼	▲	▲	▲	▲	▲	▲	▲	▲
Danazol	▼	▲	▲	▲	▲	▲	▲	▲	▲
Oxymesterone	▼	▲	▲	▲	▲	▲	▲	▲	▲

*Key: HDL-C = High-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; RBC = red blood cell; AST = aspartate aminotransferase, formerly SGOT; SGOT = serum glutamic-oxaloacetic transaminase; ALT = alanine aminotransferase, formerly SGPT; SGPT = serum glutamic-pyruvic transaminase; Alk PO_4 = alkaline phosphatase; BUN = blood urea nitrogen; ▲ = increased; ▼ = decreased.

Table 7
Antiulcer Medication Effect on Clinical Laboratory Results

Medication	Test					
	AST/ SGOT*	ALT/ SGPT	Alkaline phosphatase	Creatinine	WBC	Plt
Cimetidine	▲	▲		▲	▼	▼
Misprostol	▲	▲	▲			
Ranitidine hydrochloride		▲				

*Key: AST = aspartate aminotransferase, formerly SGOT; SGOT = serum glutamic-oxaloacetic transaminase; ALT = alanine aminotransferase, formerly SGPT; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count; Plt = platelets; ▲ = increased; ▼ = decreased.

Table 8
Antiseizure Medication Effect on Clinical Laboratory Results

Medication	Test							
	AST/ SGOT*	ALT/ SGPT	Alk PO_4	Thyroid function	Na	GGT	Glucose	Neutrophils
Carbamazepine	▲	▲	▲	▼	▼			▼
Primidone								
Phenytoin			▲			▲	▲	

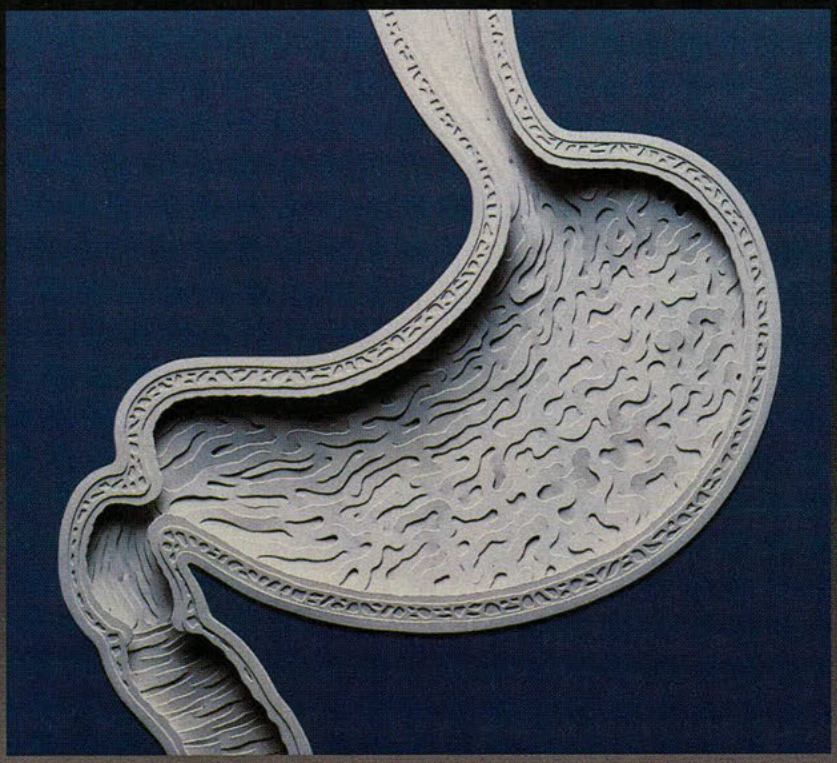
*Key: AST = aspartate aminotransferase, formerly SGOT; SGOT = serum glutamic-oxaloacetic transaminase; ALT = alanine aminotransferase, formerly SGPT; SGPT = serum glutamic-pyruvic transaminase; Alk PO_4 = alkaline phosphatase; Na = sodium; GGT = gamma glutamyl transferase; ▲ = increased; ▼ = decreased.

(continued on page 365)

In arthritis therapy:

Because you're concerned about G.I. reactions...

NSAIDs may adversely affect the hematologic, hepatic, renal, and gastrointestinal systems, although G.I. reactions occur most frequently.



Start with

25·50·75-MG TABLETS

Voltaren®

diclofenac sodium

*An established record of G.I. tolerability.**

**Contraindicated in patients hypersensitive to aspirin, other NSAIDs, or Voltaren. As with other NSAIDs, the most frequent complaints relate to the G.I. tract. In patients treated chronically with NSAID therapy, serious G.I. toxicity such as bleeding, ulceration, and perforation can occur. Elevations of SGOT and/or SGPT, some significant, have been reported in association with Voltaren treatment; cases of severe hepatic reactions have rarely been reported.*

Please see following page for brief summary of Prescribing Information.

Voltaren®
diclofenac sodium

Enteric-Coated Tablets

Brief Summary (See full Prescribing Information)

INDICATIONS AND USAGE
Voltaren is indicated for acute and chronic treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

CONTRAINDICATIONS
Patients with hypersensitivity to it, in whom Voltaren, aspirin, or other nonsteroidal anti-inflammatory drugs induce asthma, urticaria, or other allergic-type reactions.

WARNINGS
Gastrointestinal Effects
Risk of G.I. ulcerations, bleeding and perforation with nonsteroidal anti-inflammatory therapy: Serious G.I. toxicity can occur at any time, with or without warning symptoms, during chronic treatment. The occurrence is about 1% after 3-6 months, 2-4% after a year. Patients should be informed of signs and symptoms of serious G.I. toxicity and what to do if it occurs. No subset of patients not at risk has been identified. Prior history of serious G.I. events and other risk factors of peptic ulcer disease, e.g., alcoholism, smoking, etc., have been associated with increased risk. The elderly and debilitated tolerate ulceration and bleeding less well than other individuals and most spontaneous reports of fatal G.I. events are in this population. G.I. ulceration and bleeding can occur without warning symptoms and chronically treated patients should be followed. It is recommended that patients be maintained on the lowest dose of diclofenac sodium possible consistent with achieving a satisfactory therapeutic response.

Hepatic Effects
As with other nonsteroidal anti-inflammatory drugs, elevations of one or more liver tests may occur during Voltaren therapy. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations, (i.e., 1.2-3 times the upper limit of normal [ULN]), or greater elevations of transaminases occurred in about 15% of Voltaren-treated patients. The SGPT (ALT) test is probably the most sensitive indicator of liver injury. In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of SGOT (SGPT was not measured in all studies) occurred in about 2% of approximately 5700 patients at some time during Voltaren treatment. In a large, open, controlled trial, meaningful elevations of SGOT and/or SGPT occurred in about 4% of 3700 patients treated for 2-6 months, including marked elevations (i.e., more than 8 times the ULN) in about 1% of the 3700 patients. In that open-label study, a lower incidence of borderline (1.2-3 times the ULN), moderate (3-8 times the ULN), and marked (>8 times the ULN) elevations of SGOT or SGPT was observed in patients randomized to other NSAIDs. Transaminase elevations were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis (see ADVERSE REACTIONS).

Transaminase elevations were reversible on cessation of therapy, and among 51 patients in all studies with marked elevations, signs and symptoms of liver disease occurred in only 3 cases, and only 1 patient developed jaundice. Most patients with borderline elevations did not have therapy interrupted; transaminase elevations in most of these cases disappeared or did not progress. There were no identifying features to distinguish those patients who developed marked elevations from those who did not.

In addition to the enzyme elevations seen in clinical trials, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, have been reported.

Because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms, physicians should measure transaminases periodically in patients receiving long-term therapy with Voltaren. The optimum times for making the first and subsequent transaminase measurements are not known. In the largest U.S. trial (open-label), which involved 3700 patients monitored first at 8 weeks and 1200 patients monitored again at 24 weeks, almost all meaningful elevations in transaminases were detected before patients became symptomatic. In 42 of the 51 patients in all trials who developed marked transaminase elevations, abnormal tests occurred during the first 2 months of therapy with Voltaren. Based on this experience the first transaminase measurement should be made no later than 8 weeks after the start of Voltaren treatment. As with other NSAIDs, if abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), Voltaren should be discontinued.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and "flu-like" symptoms), and the appropriate action to take should these signs and symptoms appear.

PRECAUTIONS
Allergic Reactions: As with other nonsteroidal anti-inflammatory drugs, allergic reactions including anaphylaxis, have been reported.

Fluid Retention and Edema: Fluid retention and edema have been observed in some patients taking Voltaren.

Renal Effects: Cases of significant renal failure in patients receiving Voltaren have been reported from postmarketing experience, but were not observed in over 4,000 patients in clinical trials during which serum creatinines and BUNs were followed serially. Since Voltaren metabolites are eliminated primarily by the kidneys, patients with significantly impaired renal function should be more closely monitored than subjects with normal renal function.

Porphyria: The use of diclofenac in patients with hepatic porphyria should be avoided.

Drug Interactions
Aspirin: Concomitant administration of Voltaren and aspirin is not recommended.

Anticoagulants: NSAIDs affect platelet function as well, concurrent therapy with all NSAIDs, including Voltaren, and warfarin requires close monitoring of patients to be certain that no change in their anticoagulant dosage is required.

Digoxin, Methotrexate, Cyclosporine: Voltaren, like other NSAIDs, through effects on renal prostaglandins, may cause increased toxicity of digoxin, methotrexate, and cyclosporine.

Lithium: Voltaren decreases lithium renal clearance and increases lithium plasma levels. In patients taking Voltaren and lithium concomitantly, lithium toxicity may develop.

Oral Hypoglycemics: Physicians should consider the possibility that diclofenac may alter a diabetic patient's response to insulin or oral hypoglycemic agents.

Diuretics: Voltaren and other NSAIDs can inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels.

Other Drugs: In small groups of patients (7-10/interaction study), the concomitant administration of azathioprine, gold, chloroquine, D-penicillamine, prednisolone, doxycycline, or digitoxin did not significantly affect the peak levels and AUC values of Voltaren.

Drug/Laboratory Test Interactions
Effect on Blood Coagulation: Voltaren increases platelet aggregation time but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen, or factors V and VII to XII.

Pregnancy Category B
There are no adequate and well-controlled studies in pregnant women. Voltaren should be used during pregnancy only if the benefits to the mother justify the potential risk to the fetus. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), use of Voltaren during late pregnancy should be avoided.

Labor and Delivery
The effects of Voltaren on labor and delivery in pregnant women are unknown. However, as with other nonsteroidal anti-inflammatory drugs, it is possible that Voltaren may inhibit uterine contraction.

Nursing Mothers
Voltaren has been found in the milk of nursing mothers. As with other drugs that are excreted in milk, Voltaren is not recommended for use in nursing women.

Pediatric Use
Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS
The incidence of common adverse reactions (greater than 1%) is based upon controlled clinical trials in 1543 patients treated up to 13 weeks. By far the most common adverse effects were gastrointestinal symptoms, most of them minor, occurring in about 20%, and leading to discontinuation in about 3%, of patients. Peptic ulcer or G.I. bleeding occurred in clinical trials in less than 1% of approximately 1800 patients during their first 3 months of diclofenac treatment and in less than 2% of approximately 800 patients followed for 1 year. Comparative rates were 0.2% for peptic ulcer or G.I. bleeding in approximately 2000 diclofenac-treated patients and 0.6% in approximately 600 aspirin-treated patients.

In double-blind trials there were fewer minor gastrointestinal complaints in 1227 patients treated with Voltaren than in 721 patients treated with aspirin, 22% vs 33% (compared to 13% on placebo).

The following adverse reactions were reported in patients treated with Voltaren:

Incidence Greater Than 1% (All derived from clinical trials.)

Body as a Whole: Abdominal pain or cramps*, headache*, fluid retention, abdominal distention.

Digestive: Diarrhea*, indigestion*, nausea*, constipation*, flatulence, liver test abnormalities, PUB, i.e., peptic ulcer, with or without bleeding and/or perforation, or bleeding without ulcer (see above and also WARNINGS).

Nervous System: Dizziness.

Skin and Appendages: Rash, pruritus.

Special senses: Tinnitus.

*Incidence, 3% to 9% (incidence of unmarked reactions is 1-3%)

Incidence Less Than 1%—Causal Relationship Probable (Adverse reactions reported only in the literature, not seen in clinical trials, are considered rare and are italicized.)

Body as a Whole: Malaise, swelling of lips and tongue, photosensitivity, *anaphylaxis*, anaphylactoid reactions.

Cardiovascular: Hypertension, congestive heart failure.

Digestive: Vomiting, jaundice, melena, aphthous stomatitis, dry mouth and mucous membranes, bloody diarrhea, hepatitis, appetite change, pancreatitis with or without concomitant hepatitis, *colitis*.

Hemic and Lymphatic: Hemoglobin decrease, leukopenia, thrombocytopenia, *hemolytic anemia, aplastic anemia, agranulocytosis,* purpura, *allergic purpura.*

Metabolic and Nutritional Disorders: Azotemia.

Nervous System: Insomnia, drowsiness, depression, diplopia, anxiety, irritability.

Respiratory: Epistaxis, asthma, laryngeal edema.

Skin and Appendages: Alopecia, urticaria, eczema, dermatitis, *bullous eruption, erythema multiforme major,* angioedema, *Stevens-Johnson syndrome.*

Special Senses: Blurred vision, taste disorder, reversible hearing loss, scotoma.

Urogenital: *Nephrotic syndrome,* proteinuria, *oliguria, interstitial nephritis, papillary necrosis, acute renal failure.*

Incidence Less Than 1%—Causal Relationship Unknown (Adverse reactions reported only in the literature, not seen in clinical trials, are considered rare and are italicized.)

Body as a Whole: Chest pain.

Cardiovascular: Palpitations, *flushing,* tachycardia, premature ventricular contractions, myocardial infarction.

Digestive: Esophageal lesions.

Hemic and Lymphatic: *Bruising.*

Metabolic and Nutritional Disorders: Hypoglycemia, *weight loss.*

Nervous System: Paresthesia, memory disturbance, nightmares, tremor, tic, *abnormal coordination,* convulsions, *disorientation, psychotic reaction.*

Respiratory: Dyspnea, hyperventilation, edema of pharynx.

Skin and Appendages: Excess perspiration, *exfoliative dermatitis.*

Special Senses: Vitreous floaters, night blindness, amblyopia.

Urogenital: Urinary frequency, nocturia, hematuria, impotence, vaginal bleeding.

C91-8 (Rev. 4/91)

References:
1. *Kolodny AL. Two double blind trials of diclofenac sodium with aspirin and with naproxen in the treatment of patients with rheumatoid arthritis.* J Rheumatol. *1988;15:1205-1211.*
2. *Data on file, CIBA-GEIGY Pharmaceuticals.*

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leukopenia and thrombocytopenia. Misprostol has been shown to increase liver enzyme levels, but has no effect on leukocytes or platelets. Ranitidine hydrochloride has no appreciable effect on leukocytes or platelets, but does increase alanine aminotransferase (ALT) (also called serum glutamic-pyruvic transaminase [SGPT]) levels and can cause a false-positive urine protein level.

Antiseizure medication

The effects of antiseizure agents are summarized in *Table 8*.

Carbamazepine, one of the most commonly prescribed antiseizure medications, has been shown to increase liver enzyme levels, decrease thyroid function tests, increase sodium levels, and cause neutropenia and aplastic anemia. Primidone is one of the safer antiseizure medications in that it can only cause megaloblastic anemia. Phenytoin (with or without sodium) has been shown to cause increased alkaline phosphatase levels, as well as gamma glutamyl transferase and serum glucose levels.

Antibiotics

Table 9 summarizes the effects of antibiotics on laboratory tests.

Cefadroxil monohydrate, one of the cephalosporins, has been shown to increase liver enzyme levels, as well as cause a false-positive direct Coombs' test result. Cefixime can cause false-positive urine ketone or urine sugar levels. It has also been shown to cause a false-positive direct Coombs' test result. Cefoperazone sodium can cause elevated serum liver enzymes as well as BUN and creatinine levels. This medication has also been shown to cause false-positive urine sugar levels and prolonged prothrombin time. Ceftriaxone sodium

Table 9
Antibiotic Effects on Clinical Laboratory Results

Medication	Test												
	AST/ SGOT*	ALT/ SGPT	Alk PO_4	BUN	Creat	Trigl	Chol	Gluc	K	Urine ketones	Urine sugar	PT	Direct Coombs' test
Cefadroxil monohydrate	▲	▲											▲
Cefixime										▲	▲		▲
Cefoperazone sodium	▲	▲	▲	▲	▲						▲	▲	
Ceftriaxone sodium	▲	▲		▲	▲							▲	
Cephalexin											▲		▲
Ciprofloxacin						▲	▲	▲	▲			▲	
Doxycycline				▲								▼	
Erythromycin	▲	▲	▲										
Fluconzaole	▲	▲											
Penicillin	▲	▲									▲		

*Key: AST = aspartate aminotransferase, formerly SGOT; SGOT = serum glutamic-oxaloacetic transaminase; ALT = alanine aminotransferase, formerly SGPT; SGPT = serum glutamic-pyruvic transaminase; Alk PO_4 = alkaline phosphatase; BUN = blood urea nitrogen; Creat = creatinine; Trigl = triglycerides; Chol = cholesterol; Gluc = glucose; K = potassium; PT = prothrombin time; ▲ = increased; ▼ = decreased.

Table 10
Antihistamine Effects on Clinical Laboratory Results

Medication	Test				Finding	
	AST/ SGOT*	ALT/ SGPT	WBC	Neutrophil count	Platelet count	Hemolytic anemia
Terfenadine	▲	▲				
Chlorpheniramine			▼	▼	▼	▲

*Key: AST = aspartate aminotransferase, formerly SGOT; SGOT = serum glutamic-oxaloacetic transaminase; ALT = alanine aminotransferase, formerly SGPT; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count; ▲ = increased; ▼ = decreased.

can also cause increases in liver enzymes and serum BUN and creatinine levels as well as a prolonged prothrombin time. Cephalexin (with or without hydrochloride) can cause a false-positive urine sugar level and false-positive direct Coombs' test result.

Ciprofloxacin, a fluroquinolone, causes elevated serum triglyceride, cholesterol, glucose, and potassium levels, and can cause prolongation of the prothrombin time. Doxycycline (with or without a salt [calcium, hyclate, monohydrate]), one of the tetracyclines, elevates BUN levels and decreases serum prothrombin times. Erythromycin (with or without one of its various salts), one of the macrolides, causes increased serum liver enzyme levels. Fluconazole, an antifungal medication, which is becoming more popular, can cause elevated liver enzyme levels. Penicillin and clavulinic acid, a popular antibiotic used to treat infection caused by β-lactamase–producing bacteria, can cause elevated liver enzyme levels as well as a false-positive urine sugar level.

Antihistamines

Refer to *Table 10* for a summary of the effects of antihistamines.

Terfenadine has been shown to increase serum liver enzyme levels. Chlorpheniramine can cause leukopenia, neutropenia, thrombocytopenia, and hemolytic anemia.

Vitamins

Table 11 summarizes the effects of vitamins on the results of laboratory tests.

Table 11
Vitamin Effects on Clinical Laboratory Results

Medication	Test		
	AST/ SGOT*	ALT/ SGPT	Uric acid
Vitamin B_3 (niacin)	▲	▲	
Vitamin C (ascorbic acid)			▲

*Key: AST = aspartate aminotransferase, formerly SGOT; SGOT = serum glutamic-oxaloacetic transaminase; ALT = alanine aminotransferase, formerly SGPT; SGPT = serum glutamic-pyruvic transaminase; ▲ = increased; ▼ = decreased.

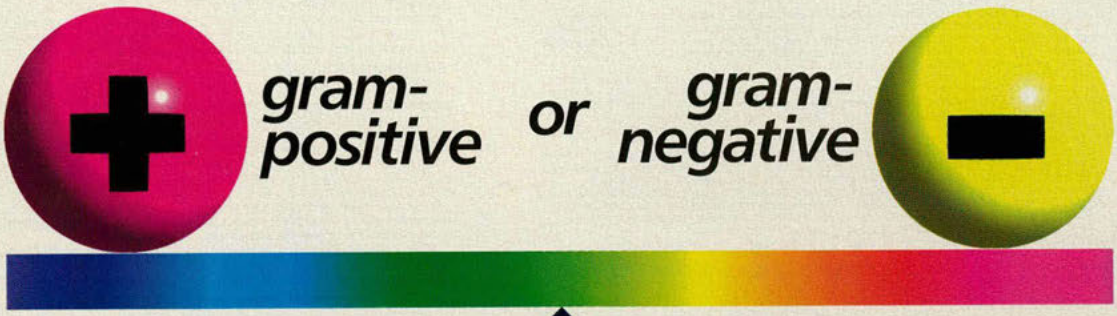
Vitamin B3 (niacin), an agent that has been long used as a lipid-lowering agent, has been shown to increase liver enzyme levels. Vitamin C (ascorbic acid), one of the commonly abused vitamins, can cause increased serum uric acid levels.

Comment

An atypical laboratory result must be fully explained by the clinician ordering the test. The effects may be due to diet, disease, or drugs, or a combination of any two or all three factors acting in concert. The clinician must determine which of these factors is causing the observed effect on the laboratory test result. The clinician must then decide as to what further action to take in response to the observed result. Careful consultation with the clinical pathologist can often aid the clinician in the decision-making process.

(continued on page 369)

For Community-Acquired Lower Respiratory Tract Infections



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Please consult Brief Summaries of Prescribing Information for ZINACEF and CEFTIN on following page.

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Zinacef®
(sterile cefuroxime sodium, Glaxo)

Zinacef®
(cefuroxime sodium injection)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zinacef® (sterile cefuroxime sodium/cefuroxime sodium injection) product labeling.

INDICATIONS AND USAGE: Zinacef® is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. **Lower Respiratory Tract Infections**, including pneumonia, caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* spp, *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing), *Streptococcus pyogenes*, and *Escherichia coli*.
2. **Urinary Tract Infections** caused by *Escherichia coli* and *Klebsiella* spp.
3. **Skin and Skin Structure Infections** caused by *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing), *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella* spp, and *Enterobacter* spp.
4. **Septicemia** caused by *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing), *Streptococcus pneumoniae*, *Escherichia coli*, *Haemophilus influenzae* (including ampicillin-resistant strains), and *Klebsiella* spp.
5. **Meningitis** caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including ampicillin-resistant strains), *Neisseria meningitidis*, and *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing).
6. **Gonorrhea:** Uncomplicated and disseminated gonococcal infections due to *Neisseria gonorrhoeae* (penicillinase- and non-penicillinase-producing strains) in both males and females.
7. **Bone and Joint Infections** caused by *Staphylococcus aureus* (including penicillinase- and non-penicillinase-producing strains).

Clinical microbiological studies in skin and skin structure infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. Zinacef has been used successfully in these mixed infections in which several organisms have been isolated. Appropriate cultures and susceptibility studies should be performed to determine the susceptibility of the causative organisms to Zinacef.

Therapy may be started while awaiting the results of these studies; however, once these results become available, the antibiotic treatment should be adjusted accordingly. In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, Zinacef may be used concomitantly with an aminoglycoside (see PRECAUTIONS). The recommended doses of both antibiotics may be given depending on the severity of the infection and the patient's condition.

Prevention: The preoperative prophylactic administration of Zinacef may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (e.g., vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. Zinacef should usually be given one-half to 1 hour before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

Prophylactic administration is usually not required after the surgical procedure ends and should be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic administration of any antibiotic does not reduce the incidence of subsequent infections but will increase the possibility of adverse reactions and the development of bacterial resistance.

The perioperative use of Zinacef has also been effective during open heart surgery for surgical patients in whom infections at the operative site would present a serious risk. For these patients it is recommended that Zinacef therapy be continued for at least 48 hours after the surgical procedure ends. If an infection is present, specimens for culture should be obtained for the identification of the causative organism, and appropriate antimicrobial therapy should be instituted.

CONTRAINDICATIONS: Zinacef® is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS: BEFORE THERAPY WITH ZINACEF® IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO ZINACEF OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*.

Mild cases of colitis may respond to drug discontinuation alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuation or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. Other causes of colitis should also be considered.

PRECAUTIONS: Although Zinacef® rarely produces alterations in kidney function, evaluation of renal status during therapy is recommended, especially in seriously ill patients receiving the maximum doses. Cephalosporins should be given with caution to patients receiving concurrent treatment with potent diuretics as these regimens are suspected of adversely affecting renal function.

The total daily dose of Zinacef should be reduced in patients with transient or persistent renal insufficiency (see DOSAGE AND ADMINISTRATION), because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses.

As with other antibiotics, prolonged use of Zinacef may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

As with other therapeutic regimens used in the treatment of meningitis, mild-to-moderate hearing loss has been reported in a few pediatric patients treated with cefuroxime sodium. Persistence of positive CSF (cerebrospinal fluid) cultures at 18 to 36 hours has also been noted with cefuroxime sodium injection, as well as with other antibiotic therapies; however, the clinical relevance of this is unknown.

Drug/Laboratory Test Interactions: A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with Clinitest® tablets) but not with enzyme-based tests for glycosuria (e.g., Tes-Tape®). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving Zinacef.

Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of cefuroxime was found in standard laboratory tests.

Reproduction studies revealed no impairment of fertility in animals.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in mice and rabbits at doses up to 60 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Since cefuroxime is excreted in human milk, caution should be exercised when Zinacef is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below 3 months of age have not been established. Accumulation of other members of the cephalosporin class in newborn infants (with resulting prolongation of drug half-life) has been reported.

ADVERSE REACTIONS: Zinacef® is generally well tolerated. The most common adverse effects have been local reactions following IV administration. Other adverse reactions have been encountered only rarely.

Local Reactions: Thrombophlebitis has occurred with IV administration in 1 in 60 patients.

Gastrointestinal: Gastrointestinal symptoms occurred in 1 in 150 patients and included diarrhea (1 in 220 patients) and nausea (1 in 440 patients). Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

Hypersensitivity Reactions: Hypersensitivity reactions have been reported in fewer than 1% of the patients treated with Zinacef and include rash (1 in 125). Pruritus, urticaria, and positive Coombs' test each occurred in fewer than 1 in 250 patients, and, as with other cephalosporins, rare cases of anaphylaxis, drug fever, erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome have occurred.

Blood: A decrease in hemoglobin and hematocrit has been observed in 1 in 10 patients and transient eosinophilia in 1 in 14 patients. Less common reactions seen were transient neutropenia (fewer than 1 in 100 patients) and leukopenia (1 in 750 patients). A similar pattern and incidence were seen with other cephalosporins used in controlled studies.

Hepatic: Transient rise in SGOT and SGPT (1 in 25 patients), alkaline phosphatase (1 in 50 patients), LDH (1 in 75 patients), and bilirubin (1 in 500 patients) levels has been noted.

Kidney: Elevations in serum creatinine and/or blood urea nitrogen and a decreased creatinine clearance have been observed, but their relationship to cefuroxime is unknown.

In addition to the adverse reactions listed above that have been observed in patients treated with cefuroxime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Vomiting, abdominal pain, colitis, vaginitis including vaginal candidiasis, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see DOSAGE AND ADMINISTRATION). If seizures associated with drug therapy should occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Altered Laboratory Tests: Prolonged prothrombin time, pancytopenia, agranulocytosis, thrombocytopenia.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zinacef® product labeling.)

Impaired Renal Function: A reduced dosage must be employed when renal function is impaired. Dosage should be determined by the degree of renal impairment and the susceptibility of the causative organism (see Table 1 in product package insert).

HOW SUPPLIED: Zinacef® in the dry state should be stored between 15° and 30°C (59° and 86°F) and protected from light. Zinacef is a dry, white to off-white powder supplied in vials and infusion packs as follows:

NDC 0173-0352-31 750-mg* Vial (Tray of 25)
NDC 0173-0354-35 1.5-g* Vial (Tray of 25)
NDC 0173-0353-32 750-mg* Infusion Pack (Tray of 10)
NDC 0173-0356-32 1.5-g* Infusion Pack (Tray of 10)
NDC 0173-0400-00 7.5-g* Pharmacy Bulk Package (Tray of 6)

Zinacef frozen as a premixed solution of cefuroxime sodium should not be stored above -20°C. Zinacef is supplied frozen in 50-mL, single-dose, plastic containers as follows:

NDC 0173-0424-00 750-mg* Plastic Container (Carton of 24)
NDC 0173-0425-00 1.5-g* Plastic Container (Carton of 24)

*Equivalent to cefuroxime.

B1-129
February 1991

Glaxo Pharmaceuticals™
DIVISION OF GLAXO INC.

Zinacef® (sterile cefuroxime sodium): Glaxo Pharmaceuticals, Research Triangle Park, NC 27709

Zinacef® (cefuroxime sodium injection): Manufactured for Glaxo Specialties Inc., Research Triangle Park, NC 27709 by Baxter Healthcare Corporation, Deerfield, IL 60015

Ceftin® (cefuroxime axetil) Tablets

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Ceftin® (cefuroxime axetil) Tablets product labeling.

INDICATIONS AND USAGE: Ceftin® Tablets are indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. **Pharyngitis and Tonsillitis** caused by *Streptococcus pyogenes* (group A beta-hemolytic streptococci). (Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Ceftin Tablets are generally effective in the eradication of streptococci from the oropharynx. Ceftin Tablets are not indicated for the prophylaxis of subsequent rheumatic fever because data to support such use are not yet available.)
2. **Otitis Media** caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (ampicillin-susceptible and ampicillin-resistant strains), *Moraxella catarrhalis* (ampicillin-susceptible strains), and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).
3. **Lower Respiratory Tract Infections** (bronchitis) caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (ampicillin-susceptible strains), and *Haemophilus parainfluenzae* (ampicillin-susceptible strains).
4. **Urinary Tract Infections** caused by *Escherichia coli* and *Klebsiella pneumoniae* in the absence of urological complications.
5. **Skin and Skin Structure Infections** caused by *Staphylococcus aureus* and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).

Bacteriologic studies to determine the causative organism and its susceptibility to cefuroxime should be performed. Therapy may be started while awaiting the results of these studies. Once these results become available, antibiotic treatment should be adjusted accordingly.

CONTRAINDICATIONS: Ceftin® Tablets are contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS: BEFORE THERAPY WITH CEFTIN® TABLETS IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFTIN TABLETS OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

As with other cephalosporins (and other broad-spectrum antibiotics), pseudomembranous colitis has been reported with the use of Ceftin; therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*.

Mild cases of colitis may respond to drug discontinuation alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. Elderly patients may be susceptible to fluid losses and should be treated aggressively. Antiperistaltic agents such as opiates and diphenoxylate with atropine (e.g., Lomotil®) may prolong and/or worsen the condition and should be avoided if pseudomembranous colitis is suspected.

When the colitis is not relieved by drug discontinuation or when it is severe, metronidazole and oral vancomycin have been shown to be beneficial. Oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. Other causes of colitis should also be considered.

PRECAUTIONS: General: If an allergic reaction to Ceftin® Tablets occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., antihistamines, pressor amines, or corticosteroids.

As with other antibiotics, prolonged use of Ceftin Tablets may result in overgrowth of nonsusceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Broad-spectrum antibiotics should be prescribed with caution for individuals with a history of colitis.

Information for Patients: (Pediatric) Ceftin is only available in tablet form. During clinical trials, the tablet was well tolerated by children who could swallow the tablet whole. Children who cannot swallow the tablet whole may have the tablet crushed and mixed with food (e.g., applesauce, ice cream). However, it should be noted that the crushed tablet has a strong, persistent, bitter taste. Discontinuation of therapy due to the taste and/or problems of administering this drug occurred in 13% of children (range, 2% to 28% across centers). Thus, the physician and parent should ascertain, preferably while still in the physician's office, that the child can ingest Ceftin Tablets reliably. If not, alternative therapy should be considered.

Drug/Laboratory Test Interactions: A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with Clinitest® tablets), but not with enzyme-based tests for glycosuria (e.g., Clinistix®, Tes-Tape®). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving Ceftin Tablets.

Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of cefuroxime was found in standard laboratory tests.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy: ***Pregnancy Category B:*** Reproduction studies have been performed in rats and mice at doses up to 50 to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime axetil. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Since cefuroxime is excreted in human milk, consideration should be given to discontinuing nursing temporarily during treatment with Ceftin Tablets.

ADVERSE REACTIONS: The adverse reactions to Ceftin® Tablets are similar to reactions to other orally administered cephalosporins. Ceftin Tablets were usually well tolerated in controlled clinical trials. Pediatric patients taking crushed tablets during clinical trials complained of the bitter taste of Ceftin Tablets (see ADVERSE REACTIONS: Gastrointestinal and PRECAUTIONS: Information for Patients: (Pediatric)). The majority of adverse events were mild, reversible in nature, and did not require discontinuation of the drug. The incidence of gastrointestinal adverse events increased with the higher recommended doses. Twenty-five (25) patients have received Ceftin Tablets 500 mg twice a day for one to 2.5 months with no increase in frequency or severity of adverse events.

The following adverse reactions have been reported.

Gastrointestinal: Nausea occurred in 2.4% of patients. Vomiting occurred in 2.0% of patients. Diarrhea occurred in 3.5% of patients. Loose stools occurred in 1.3% of patients. There have been reports of pseudomembranous colitis (see WARNINGS).

Crushed tablets have a bitter taste. In pediatric clinical studies conducted with crushed tablets, complaints due to taste ranged from 0/8 (0%) in one center to 47/71 (66%) in another center.

Hypersensitivity: Rash (0.6% of patients), pruritus (0.3% of patients), and urticaria (0.2% of patients) have been observed. One case of severe bronchospasm has been reported among the approximately 1,600 patients treated with Ceftin Tablets. Of the patients treated with Ceftin Tablets who reported a history of delayed hypersensitivity to a penicillin and not a cephalosporin, 2.9% of patients experienced a delayed hypersensitivity reaction to Ceftin Tablets.

As with other cephalosporins, hypersensitivity reactions including Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, drug fever, and anaphylaxis have been reported.

Central Nervous System: Headache occurred in less than 0.7% of patients, and dizziness occurred in less than 0.2% of patients.

Other: Vaginitis occurred in 1.9% of female patients.

Clinical Laboratory Tests: Transient elevations in AST (SGOT, 2.0% of patients), ALT (SGPT, 1.6% of patients), and LDH (1.0% of patients) have been observed. Eosinophilia (1.1% of patients) and positive Coombs' test (0.4% of patients) have been reported.

In addition to the adverse reactions listed above that have been observed in patients treated with Ceftin Tablets, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Allergic reactions including colitis, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, abdominal pain, superinfection, aplastic anemia, hemolytic anemia, hemorrhage, and pain and/or phlebitis at the injection site.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. If seizures associated with drug therapy should occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Altered Laboratory Tests: Increased prothrombin time, increased BUN, increased creatinine, false-positive test for urinary glucose, increased alkaline phosphatase, neutropenia, thrombocytopenia, leukopenia, elevated bilirubin, pancytopenia, and agranulocytosis.

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B1-420
February 1991

ZN2010 Printed in USA October 1991

Acknowledgment

Thanks are expressed to Mrs Ollie Margie for her assistance in the preparation of this article.

Bibliography

Cooper JW: Reviewing geriatric concerns with commonly used drugs. *Geriatrics* 1989;44(12):79-86.

Dipalma JR: Antihypertensive drugs and serum cholesterol levels. *Am Fam Physician* 1988;40:217-219.

Hough DO, Voy RO: When to suspect steroid abuse. *Patient Care* Aug 15, 1990;24:129-132,134,136.

King JS: Clinical chemistry-effects of drugs on clinical laboratory tests. *J Am Assn Clin Chem* 1975;21(5):1D-432D.

1991 Physicians' Desk Reference, ed 45. Oradell, NJ, Medical Economics Data, 1991.

Sadat A, Paulman PM, Mathews M: Hypernatremia in the elderly. *Am Fam Physician* 1989;40:125-128.

Scheier R, Briner VA: The differential diagnosis of hyponatremia. *Hosp Pract*, Sept 30, 1990;25:29-37.

Schwartz AB, Cannon-Babb M: Hyperkalemia due to drugs in diabetic patients. *Am Fam Physician* 1989;39:225-231.

Shulkin D, Detore AW: When laboratory tests are abnormal and the patient feels fine. *Hosp Pract*, July 15, 1990;25:85-92.

Vidt DG, Borazanian RA: Calcium channel blockers in geriatric hypertension. *Geriatrics* 1991;46(1):28-38