From the FDA

OTC acne treatment investigated

Benzoyl peroxide, a common antibacterial ingredient in over-the-counter acne products, may prompt precancerous tumors to become malignant.

According to the agency, benzoyl peroxide is a "potent skin tumor promoter in more than one strain of mice and other laboratory animals tested." Because of this finding, the agency has revoked the "safe and effective" finding associated with the drug and called for further testing.

A panel of scientists is expected to meet later this year to decide whether this active ingredient should be removed from the market while further testing is ongoing. The additional testing is expected to take 2 years before final results are available.

Advisory panel calls for more breast implant data

Four manufacturers of breast implants have failed to provide adequate information concerning the safety of their products, concluded the General and Plastic Surgery Devices [Advisory] Panel.

Chairperson Elizabeth Connell, MD, emphasized that the panel's recommendation does not mean the implants are unsafe, only that insufficient data concerning the implants' risks and benefits were available. However, panel members did recommend keeping the implants on the market until the agency receives further data from the breast implant manufacturers.

Food label changes proposed

Under the Nutrition Labeling and Education Act of 1990, the agency has proposed stricter guidelines for food manufacturers to follow. Nutritional information that must appear on the label includes calories from total fat, total fat (in grams), saturated fat (in grams), cholesterol (in milligrams), total carbohydrates (in grams), complex carbohydrates (in grams), sugars (in grams), dietary fiber (in grams), protein (in grams), sodium (in milligrams), vitamin A (percent of daily value), vitamin C (percent of daily value), calcium (percent of daily value), and iron (percent of daily value).

Serving sizes would be defined as those portions customarily consumed by persons aged 4 years and older. Specific serving sizes would be measured according to cups, tablespoons, and teaspoons.

Uniform definitions for descriptive terms have been proposed, as well. For example, those words used to describe the fat content of foods are described accordingly:
Fat-free: Contains less than 0.5 g of fat per serving with no added fat or oil; *Low-fat* Contains no more than 3 g of fat per reference amount; *Light (or lite)*: Product has at least one-third fewer calories than the regular version of the same product; *Reduced fat*: Fat content has been reduced by 50% or more; *Less fat*: Product has at least 25% less fat than comparative food, with a minimum 3-g fat reduction per reference amount or serving.

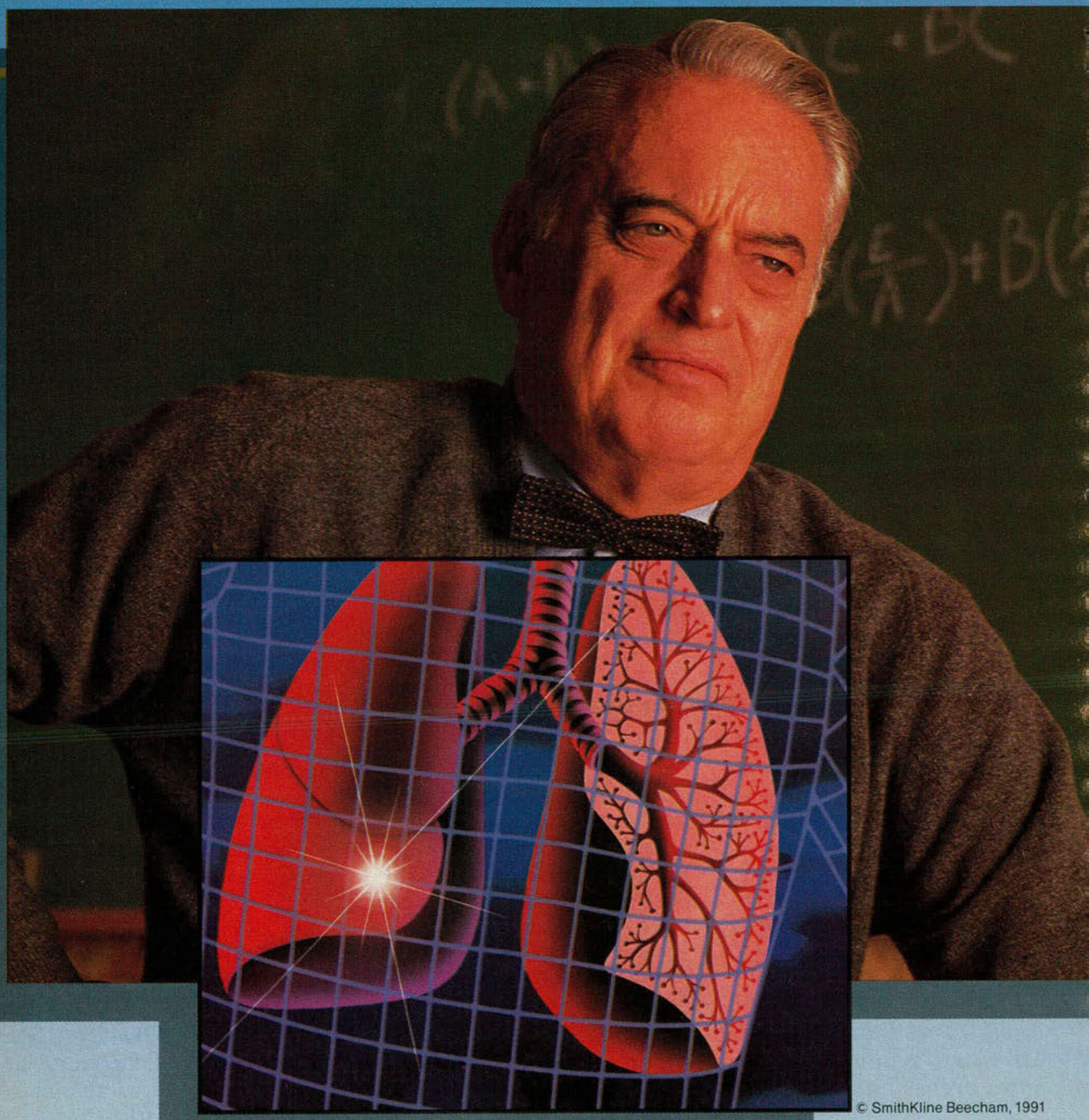
Under the new guidelines, food manufacturers would be allowed to make health claims if a link has already been established between a nutrient contained in that product and a specific disease, such as calcium and prevention of osteoporosis. No other nutrient found in the same product must be linked with an increase in disease. Fat-laden cooking oil, for example, could not be touted as a cholesterol-free product.

These proposed guidelines, which have also been adopted by the Department of Agriculture for meat and dairy products, are scheduled to go into effect in May 1993. However, manufacturers may voluntarily comply with the proposals before then.

(continued on page 46)

IN LOWER RESPIRATORY INFECTIONS

Your patients deserve first-time success*...



Brief Summary of Prescribing Information

AUGMENTIN amoxicillin/clavulanate potassium

Indications and Usage: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower Respiratory Infections caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.

Otitis Media caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.

Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.

Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.

Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Augmentin should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential. **Pregnancy (Category B):** Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to

Prescribe 1 AUGMENTIN®

amoxicillin/clavulanate potassium

First-line for all the right reasons

*Clinical success rate for bronchitis and pneumonia was 98%. Data on file, Medical Department, SmithKline Beecham Pharmaceuticals.

Augmentin. 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.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See Warnings).

Liver: A moderate rise in SGOT, SGPT, AST, and/or ALT has been noted in patients treated with ampicillin class antibiotics including *Augmentin*. The significance of these findings is unknown. As with some other penicillins and some cephalosporins, hepatic dysfunction has been reported rarely, with the predominant effects being cholestatic, hepatocellular, or mixed cholestatic-hepatocellular. Signs/symptoms may appear during or after therapy and they resolve completely over time.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Dosage: Adults: The usual adult dose is one *Augmentin* '250' tablet every eight hours. For more severe infections and infections of the respiratory tract, the dose should be one *Augmentin* '500' tablet every eight hours.

Since both the *Augmentin* '250' and '500' tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two *Augmentin* '250' tablets are not equivalent to one *Augmentin* '500' tablet. Therefore, two *Augmentin* '250' tablets should not be substituted for one *Augmentin* '500' tablet for treatment of more severe infections.

Children: The usual dose is 20 mg/kg/day, based on amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis and other more severe infections, the dose should be 40 mg/kg/day, based on the amoxicillin component, in divided doses every eight hours. Also available as *Augmentin* '125' and '250' chewable tablets.

Children weighing 40 kg and more should be dosed according to the adult recommendations.

BRS-AG:L1 9417095

SB
SmithKline Beecham
Pharmaceuticals

Philadelphia, PA 19101

Revamped drug approval process proposed

The Council on Competitiveness, chaired by Vice President Dan Quayle, has proposed reforming the drug review system. The Council's report, prepared under the direction of Constance Horner, former Health and Human Services deputy secretary, recommends the following changes in the current system:

- Expand the drug review process using nongovernment scientific experts contracted with the FDA. The additional scientists would augment the agency's reviewers, eliminating drug application backlogs. These contracted reviewers would have to adhere to a 180-day deadline.
- Continue to maximize a drug's potential for approval by considering the risks to human life and health that may result from delay of any new treatments.
- Use "surrogate endpoints" or other evidence indicating the efficacy of a drug to accelerate the drug approval process for serious, life-threatening illnesses and conditions that lack alternative modes of therapy. Further study of the drug would be required to confirm these surrogate endpoints even after it received approval.
- Strengthen rules for removal of ineffective, unsafe drugs.
- Conform, where possible, the US revamped approval system with that found in other industrialized nations. This harmony would reduce duplicatory testing conducted in countries where the same drug is to be marketed.
- Implement various management changes, including the computerization of all drug applications by 1995 and the installation of new systems for monitoring the drug review process itself.

AIDS-related treatment receives IND status

An experimental drug (566C80) received investigational new drug (IND) status for the treatment of *Pneumocystis carinii* pneumonia. Under the IND status, 566C80 will be made available to patients with the acquired immunodeficiency syndrome (AIDS) who cannot tolerate standard treatment (trimethoprim-sulfa) for *Pneumocystis carinii* pneumonia.

The most serious side effect associated with 566C80 in clincal trials was the outbreak of severe rashes. Less serious side effects included mild rashes, fever, minor blood abnormalities, and various digestive problems.

Physicians interested in enrolling patients in this IND status program or an open-study protocol may contact Burroughs Wellcome Co (Research Triangle Park, NC) at (800) 755-2020.

CARDIZEM®

(diltiazem HCl)

PUTS YOUR ANGINA PATIENTS BACK IN ACTION*

EXTREMELY WELL TOLERATED[1]

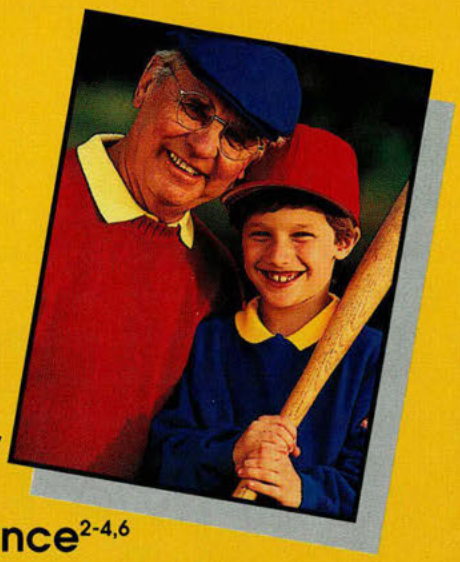
*CARDIZEM® (diltiazem HCl) is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

CAZXC567/A3121

Please see brief summary of prescribing information on next page.

6443M1

CARDIZEM®
(diltiazem HCl)



UNSURPASSED EFFICACY AND SAFETY

- **Unsurpassed reductions in the frequency of anginal episodes[2-5]**
- **Unsurpassed increases in exercise tolerance[2-4,6]**

References:
1. Data on file, Marion Merrell Dow Inc. **2.** Frishman W, Charlap S, Kimmel B, et al. *Circulation.* 1988;77:774-786. **3.** Klinke WP, Kvill L, Dempsey EE, Grace M. *J Am Coll Cardiol.* 1988;12:1562-1567. **4.** Hung J, Lamb IH, Connolly SJ, Jutzy KR, Goris ML, Schroeder JS. *Circulation.* 1983;68:560-567. **5.** L'Abbate A, Parodi O, Panciroli C, et al. *Cardiology Board Review.* 1989;6(suppl):50-54. **6.** Anderson JL, Wagner JM, Datz FL, Christian PE, Bray BE, Taylor AT. *Am Heart J.* 1984;107:698-706.

BRIEF SUMMARY

CARDIZEM®
(diltiazem hydrochloride) Tablets

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 (six of 1,243 patients for 0.48%). 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). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** 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 have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) 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, 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 or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly 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 and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

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 some reduction in early individual pup weights and survival rates. 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.

In domestic placebo-controlled angina trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies of angina patients. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences from these studies, as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular: Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, bundle branch block, congestive heart failure, ECG abnormality, flushing, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

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

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

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

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

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. There have been observed cases of a generalized rash, characterized as leukocytoclastic vasculitis. 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 definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established. Exfoliative dermatitis (proven by rechallenge) has also been reported.

Issued 1/91

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