

For Sinusitis and URI

**Deconamine<sup>®</sup> SR  
Agrees:  
You Should  
Be Able To  
Prescribe Any  
Antibiotic  
You Want.**

**Deconamine<sup>®</sup> SR has no known  
contraindications with any antibiotic...**

*Surprisingly, this is not true of all antihistamine/decongestants.*

# Deconamine<sup>®</sup> SR

(chlorpheniramine maleate, 8 mg /d-pseudoephedrine HCl, 120 mg)  
**SUSTAINED-RELEASE capsules** **Rx Only**

**Clears Nasal Congestion • Promotes Sinus Drainage**

Deconamine<sup>®</sup> SR offers onset of action within 1 hour. *Surprisingly, even some of the newer antihistamine/decongestants do not deliver this rapid onset of action.*

*Balanced antihistamine/decongestant therapy for effective, long-acting relief of sinusitis symptoms.*

- Mild CNS effect
- Low sedation<sup>1</sup>
- Lowest reported cardiotoxicity profile<sup>2</sup>

Chlorpheniramine has been rated as having a low drowsiness factor. However, all cold/flu/allergy medications may cause drowsiness in certain individuals. So, it is advisable to avoid driving a motor vehicle, operating machinery, or drinking alcoholic beverages while taking this or any similar product.

*Your Prescription Makes A World Of Difference*

Please see accompanying brief summary of Product Information.

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## References:

1. May RJ. Allergic rhinitis. *Pharmacotherapy: A Pathophysiologic Approach*. 1989;9:45-947.
2. White WB. Drugs for cough and cold symptoms in hypertensive patients. *AFP*. 1985;183-187.

Brief Summary of Product Information

**DECONAMINE**® (brand of chlorpheniramine maleate and d-pseudoephedrine HCl) **SR CAPSULES, TABLETS, SYRUP**  
Consult package insert for full Prescribing Information.

### DESCRIPTION:

**SR CAPSULES** Each sustained-release blue and yellow capsule contains:  
chlorpheniramine maleate..... 8 mg  
d-pseudoephedrine hydrochloride..... 120 mg  
The capsules are designed to provide prolonged release of medication.

**TABLETS** Each scored, white tablet contains:

chlorpheniramine maleate..... 4 mg  
d-pseudoephedrine hydrochloride..... 60 mg

**SYRUP** — No alcohol, no dye.

Each 5 mL (teaspoonful) clear, colorless to slightly yellow liquid contains:  
chlorpheniramine maleate..... 2 mg  
d-pseudoephedrine hydrochloride..... 30 mg  
in a grape-flavored, aromatic vehicle.

**INDICATIONS:** DECONAMINE<sup>®</sup> is indicated for the temporary relief of symptoms such as rhinorrhea, sneezing and nasal congestion due to upper respiratory infections (the common cold), sinusitis or allergic rhinitis; also to help clear nasal passages and shrink swollen membranes, decongest sinus openings and passages, promote sinus drainage and/or relieve sinus pressure.

**CONTRAINDICATIONS:** Patients with severe hypertension, severe coronary artery disease and patients on MAO inhibitor therapy. DECONAMINE medications are also contraindicated in patients sensitive to antihistamines or sympathomimetic agents.

**WARNINGS:** Chlorpheniramine maleate should be used with extreme caution in patients with narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, or bladder neck obstruction. Due to its mild atropine-like action, chlorpheniramine maleate should be used cautiously in patients with bronchial asthma, emphysema, or chronic pulmonary disease. May cause excitability especially in children.

Sympathomimetic amines should be used with caution in patients with hypertension, ischemic heart disease, diabetes mellitus, increased intraocular pressure, hyperthyroidism and prostatic hypertrophy. Sympathomimetics may produce central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension.

Nervousness, dizziness or sleeplessness may occur at higher doses.

**PRECAUTIONS: Information for patients:** Antihistamines may impair mental and physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. Patients should also be warned about possible additive effects with alcohol and other central nervous system depressants (hypnotics, sedatives, tranquilizers).

**Drug interactions:** Pseudoephedrine containing drugs should not be given to patients treated with monoamine oxidase (MAO) inhibitors because of the possibility of precipitating a hypertensive crisis. MAO inhibitors also prolong and intensify the anticholinergic effects of antihistamines. Sympatho-mimetics may reduce the antihypertensive effect of methylodopa, reserpine, veratrum alkaloids and mecamylamine.

Alcohol and other sedative drugs will potentiate the sedative effects of chlorpheniramine.

Care should be taken in administering DECONAMINE<sup>®</sup> medications concomitantly with other sympathomimetic amines, since their combined effects on the cardiovascular system may be harmful to the patient.

**Pregnancy:** Pregnancy Category C. Animal reproduction studies have not been conducted with DECONAMINE<sup>®</sup> medications. It is also not known whether DECONAMINE<sup>®</sup> medications can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. DECONAMINE<sup>®</sup> medications should be given to a pregnant woman only if clearly needed.

**Nursing Mothers:** Due to the possible passage of pseudoephedrine and chlorpheniramine into breast milk, and because of the higher than usual risk for infants from sympathomimetic amines and antihistamines, the benefit to the mother vs. the potential risk should be considered and a decision should be made whether to discontinue nursing or to discontinue the drug.

**Pediatric Use:** DECONAMINE<sup>®</sup> Capsules or Tablets should not be given to children under 12 years of age.

**ADVERSE REACTIONS: Chlorpheniramine maleate:** Slight to moderate drowsiness may occur and is the most frequent side effect. Other possible side effects of antihistamines in general include: *General:* urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose and throat; *Cardiovascular:* hypotension, headache, palpitation, tachycardia, extrasystoles; *Hematological:* hemolytic anemia, thrombocytopenia, agranulocytosis; *CNS:* sedation, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, hysteria, neuritis, convulsion; *Gastrointestinal:* epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation; *Genitourinary:* urinary frequency, difficult urination, urinary retention, early menses; *Respiratory:* thickening of bronchial secretions, tightness of chest, wheezing and nasal stuffiness.

**Pseudoephedrine hydrochloride:** Pseudoephedrine may cause mild central nervous system stimulation, especially in those patients who are hypersensitive to sympathomimetic drugs. Nervousness, excitability, restlessness, dizziness, weakness and insomnia may also occur. Headache and drowsiness have also been reported. Large doses may cause lightheadedness, nausea and/or vomiting. Sympathomimetic drugs have also been associated with certain untoward reactions including fear, anxiety, tenseness, restlessness, tremor, weakness, pallor, respiratory difficulty, dysuria, insomnia, hallucination, convulsion, CNS depression, arrhythmias and cardiovascular collapse with hypotension.

**OVERDOSAGE:** Acute overdosage may produce clinical signs of CNS stimulation and variable cardiovascular effects. Pressor amines should be used with great caution in the presence of pseudoephedrine. Patients with signs of stimulation should be treated conservatively.

### DOSE AND ADMINISTRATION:

**SR Capsules:** Adults and children over 12 years, 1 capsule every 12 hours. Children under 12 years, DECONAMINE<sup>®</sup> Syrup is recommended.

**Tablets:** Adults and children over 12 years, 1 tablet three or four times daily. Children under 12 years, DECONAMINE<sup>®</sup> Syrup is recommended.

**Syrup:** Children 2 to 6 years, 1/2 teaspoonful (2.5 mL) three or four times daily, not to exceed 2 teaspoonfuls in 24 hours. Children 6 to 12 years, 1/2 to 1 teaspoonful (2.5 to 5 mL) three or four times daily, not to exceed 4 teaspoonfuls in 24 hours. Adults and children over 12 years, 1 to 2 teaspoonfuls (5 to 10 mL) three or four times daily. Children under 2 years, as directed by physician.

Caution: Federal law prohibits dispensing without prescription.

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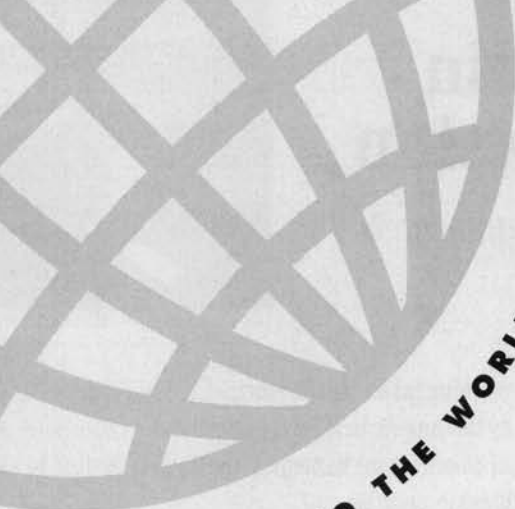
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OF

# FAMILY MEDICINE

VOL 4 NO. 10, OCTOBER 1995

Special Selections

Original Contributions

**Clinical Picture**

Tulio Bryk, MD; Zvi Weizman, MD;  
Edna Kurzbart, MD;  
Hanna Shulman, MD;  
Esther Maor, MD;  
Walter W. Tunnessen, Jr, MD

**Clinical Picture**

Karen E. Pond, MD; Henry M. Feder, Jr, MD;  
Walter W. Tunnessen, Jr, MD

Living in Medicine

**I Treated; Now I Want To Prevent**

Richard E. Waltman, MD

Letter to the Editor

**Brief Diagnostic Interviews (SDDS-PC)  
for Multiple Mental Disorders  
in Primary Care**

Lee Hyde, MD

**In Reply**

Myrna M. Weissman, PhD,  
Marjorie A. Bowman, MD, MPA

826

**Nedocromil in the Outpatient  
Management of Asthma**

Joseph M. Keenan, MD; Leonard Bielory, MD;  
Patrick C. Flamion, MD; Linda B. Ford, MD;  
Martin Murcek, MD; Dennis R. Pyszczynski, MD;  
Jay Selcow, MD; Anthony Silvagni, DO, PharmD;  
Martha Tarpay, MD; Myron J. Zitt, MD

828

**Practice Commentary**

Julienne K. Kirk, PharmD

**Food Behaviors of Southern Rural  
Community-Living Elderly**

Kathryn M. Kolasa, PhD, RD;  
Jim P. Mitchell, PhD;  
Ann C. Jobe, MD, MSN

831

**Colorectal Cancer Trends by Race  
and Anatomic Subsites, 1975 to 1991**

Kenneth C. Chu, PhD; Robert E. Tarone, PhD;  
Wong-Ho Chow, PhD; George A. Alexander, MD

833

**Prevalence of Mental Disorders  
in Primary Care: Implications  
for Screening**

Andrew C. Leon, PhD; Mark Olsson, MD;  
W. Eugene Broadhead, MD, PhD;  
James E. Barrett, MD; Robert S. Blacklow, MD;  
Martin B. Keller, MD; Edmund S. Higgins, MD;  
Myrna M. Weissman, PhD

833

835

843

844

849

857

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**Reducing Perioperative Myocardial Infarction Following Vascular Surgery: The Potential Role of  $\beta$ -Blockade**

**Objective:** To determine which perioperative variables may influence the occurrence of perioperative myocardial infarction (PMI) following vascular surgery.

**Design:** Case-control study.

**Setting:** Combined Veterans Affairs Medical Center-university hospital vascular service.

**Patients:** During a 4-year period, all major vascular surgical operations (N=2088) were evaluated with serial postoperative electrocardiography and cardiac enzyme measurements. Patients with PMI following nonemergent vascular surgery (N=53) were matched with randomly selected control patients without PMI (N=106) for age, gender, type of operation, hypertension, and symptoms of coronary artery disease.

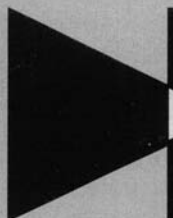
**Main Outcome Measures:** The two groups were com-

pared for operative blood loss, blood pressure, and heart rate as well as length of operation, type of anesthetic, and use of perioperative  $\beta$ -blockers, nitroglycerine, calcium channel blockers, vasopressors, and angiotensin-converting enzyme inhibitors.

**Results:**  $\beta$ -Blockers were used less frequently in patients with PMI than in control patients without PMI (30% vs 50%;  $P=.01$ ). Overall  $\beta$ -blockade was associated with a 50% reduction in PMI ( $P=.03$ ). Perioperative myocardial infarction was not associated with length of operation, type of anesthetic, blood pressure, or use of other medications.

**Conclusions:**  $\beta$ -Blockade is associated with a decreased incidence of PMI in patients undergoing vascular surgery. Prophylactic perioperative use of  $\beta$ -blockers may decrease PMI in patients requiring major vascular surgery. A prospective randomized trial of  $\beta$ -blockers in these patients appears to be warranted.

(1995;130:869-873) Richard A. Yeager, MD, et al, Portland Veterans Affairs Medical Center, Surgical Service 112P, PO Box 1034, Portland, OR 97207.



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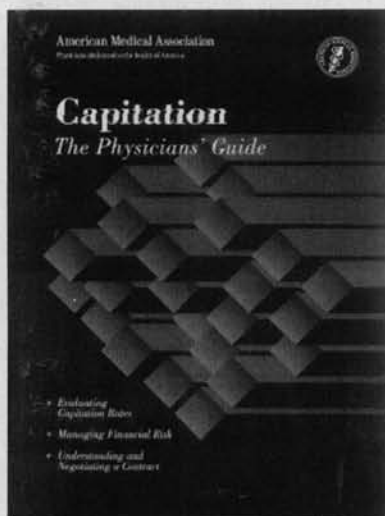
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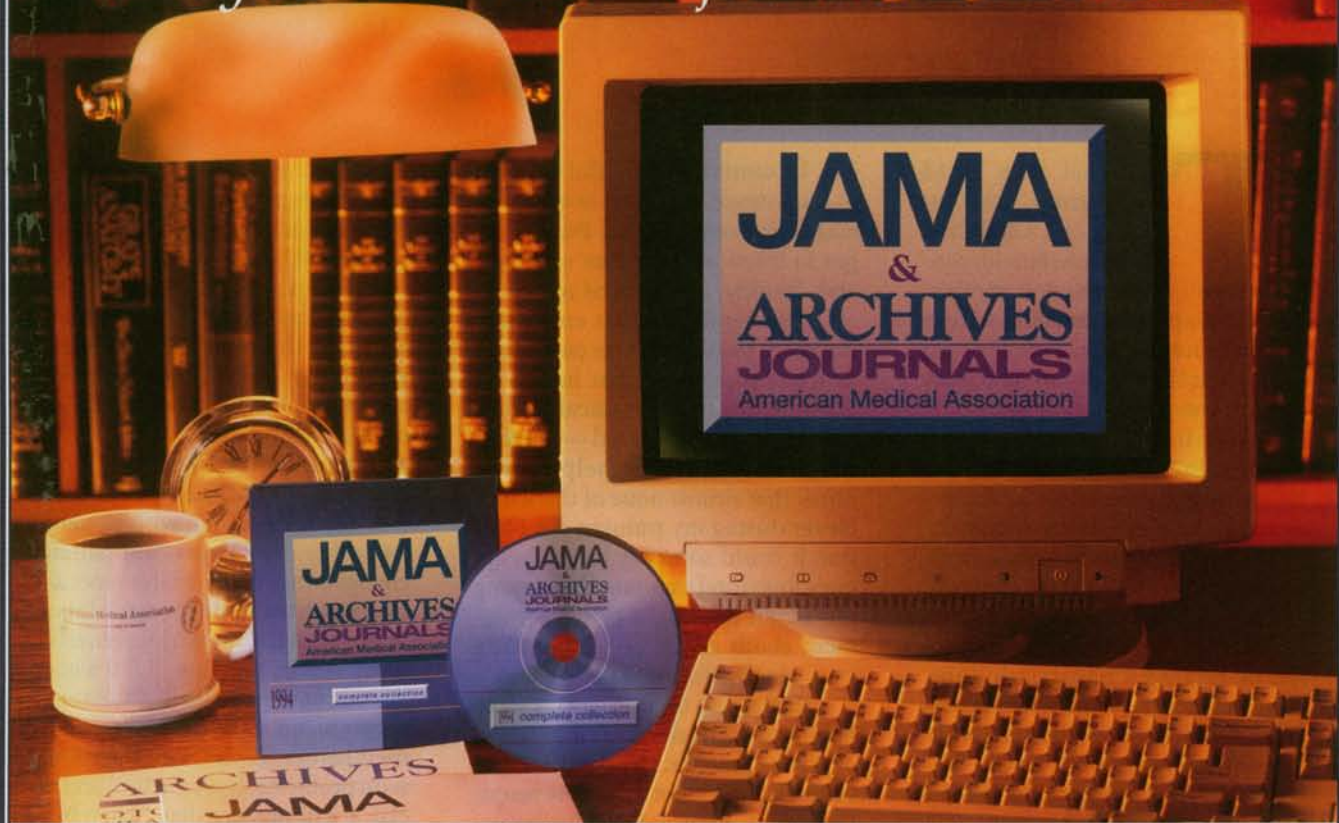
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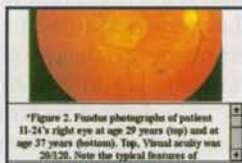


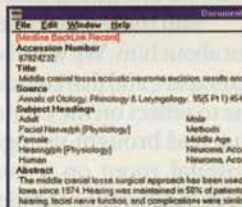
Figure 2. Fundus photographs of patient 11-24's right eye at age 29 years (top) and at age 37 years (bottom). Top, Visual acuity was 20/20. Note the typical features of

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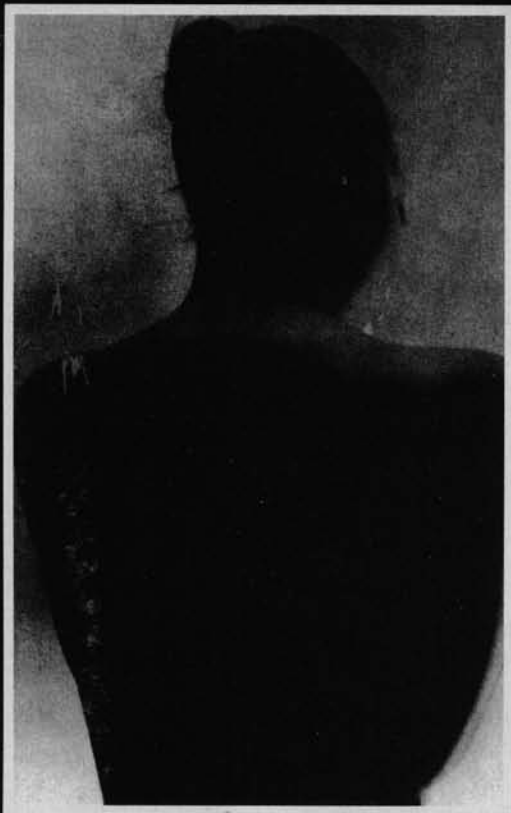
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Minimum Windows System Requirements: 386-SX, 540 KB hard disk space, 4 MB RAM, VGA monitor. Macintosh format in development. OVID Software from OVID Technologies, Inc.

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*This year,  
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If she doesn't make  
a mammogram appointment,  
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For her, it's just as simple as brushing her teeth or taking a vitamin. But if you don't remind her, she may forget about one of the simplest yet most valuable steps in taking care of herself — a mammogram.

October is National Breast Cancer Awareness Month (NBCAM). Don't let her forget. Make sure she schedules a mammogram, because early detection can find what she may not be able to feel. So you can help save her life.

NBCAM supports the Clinton Administration's Medicare Mammography Awareness Campaign which encourages Medicare-eligible women to take advantage of Medicare coverage for screening and diagnostic mammograms.

*October 19 is National Mammography Day —  
A good day for a mammogram.*



**NBCAM**

To locate a mammography facility in your area,  
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1-800-I'M AWARE

National Alliance of Breast Cancer Organizations  
(NABCO) 1-800-719-9154

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1-800-221-2141

NATIONAL BREAST CANCER AWARENESS MONTH

A message from the Board of Sponsors of National Breast Cancer Awareness Month, made possible by an educational grant from the Zeneca HealthCare Foundation.

# Patients prefer cough tablets, and so will you when you see the unique Brontex® formula.



**Patients prefer the tablet form more than 2:1 over liquids.\***

**At a 10 mg codeine dose, only Brontex provides a therapeutic level of an expectorant (per Federal guidelines)†**

**Competitors' liquids don't.**

The Federal "Cough/Cold" Monograph requires 200–400 mg of guaifenesin for a dose to be therapeutic. The 300 mg level of expectorant in Brontex, which is not available in a teaspoon of any codeine cough liquid likely due to taste and solubility limitations, is made possible by the unique tablet form. And, since the tablet form is patient-preferred, Brontex not only has the formula for you, but the form for your patients as well.

FROM THE MAKERS OF ENTEx® PRODUCTS

## Brontex®

CODEINE PHOSPHATE...10mg

(Warning: May be habit forming)

GUAIFENESIN.....300mg



**RIGHT FORM. RIGHT FORMULA.**

Because Brontex contains codeine, some patients may experience dizziness, sedation, nausea, emesis, and constipation. Please see brief summary of prescribing information on next page.

\* In a recent survey among 100 cough sufferers who took Brontex tablets and a prescription cough liquid in the past 12 months. Survey conducted via geographically dispersed pharmacies. 71% of patients expressed a preference for the tablet form, 24% of patients expressed a preference for liquid form, and 5% of patients expressed no preference for either form. Data on file.  
† The most commonly prescribed dose of most codeine/guaifenesin products is 1 teaspoon (1994 NDTI data). Recommended adult dosage for most codeine/guaifenesin products is 2 teaspoons every 4 hours.

1 Tablet  
Every  
4 Hours

# Brontex®

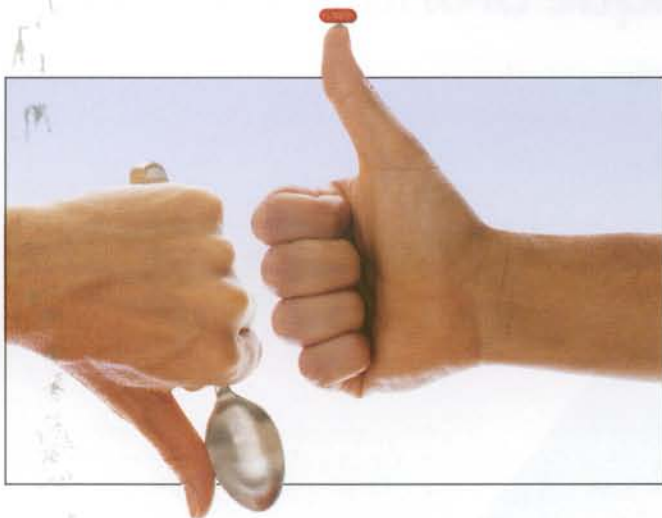
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(Warning: May be habit forming)

GUAIFENESIN.....300mg



## RIGHT FORM. RIGHT FORMULA.



## Effective cough relief in a tablet form that patients prefer more than 2:1.

At a 10 mg codeine dose, only Brontex provides a therapeutic level of an expectorant (per Federal guidelines).

Competitors' liquids don't.

#### References:

1. Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Expectorant Drug Products for Over-the-Counter Human Use; Final Monograph, Final Rule. *Federal Register*, Vol. 54, No. 38, Tuesday, February 28, 1989.

Please see brief summary of prescribing information below.

### Brontex®

(codeine phosphate/guaifenesin) tablets

**DESCRIPTION:** Each Brontex® tablet and 4 teaspoonsful (20 mL) of Brontex liquid contains codeine phosphate.....10 mg

Warning — May be habit forming

guaifenesin.....300 mg

**INDICATIONS AND USAGE:** Temporarily relieves cough due to minor throat and bronchial irritation as may occur with a cold, or inhaled irritants. Helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus.

**CONTRAINDICATIONS:** Brontex tablets are contraindicated for use in patients with asthma.

**WARNINGS:** Codeine is not recommended for use in pediatric patients under 2 years of age. Pediatric patients under 2 years may be more susceptible to the respiratory depressant effects of codeine, including respiratory arrest, coma, and death.

**PRECAUTIONS: General:** Codeine should be used with extreme caution in patients with severe CNS depression, respiratory depression, or those prone to respiratory depression, acute alcoholism, chronic pulmonary disease and those with substantially decreased respiratory reserve. Codeine should be administered with caution in patients with acute abdominal conditions, convulsive disorders, significant hepatic or renal impairment, fever, hypothyroidism, Addison's disease, ulcerative colitis, prostatic hypertrophy, in patients with recent gastrointestinal or urinary tract surgery, and in the very young or elderly or debilitated patients.

Administration of codeine may be accompanied by histamine release and should be used with caution in pediatric patients with atopy.

Dosage of codeine should not be increased if cough fails to respond; an unresponsive cough should be reevaluated in 5 days or sooner for possible underlying pathology, such as foreign body or lower respiratory tract disease.

Codeine may cause or aggravate constipation.

**Hypotensive Effects:** Codeine may produce hypotension in ambulatory patients.

**Head Injury and Increased Intracranial Pressure:** The risk of respiratory depression and elevation of cerebrospinal fluid pressure is increased by opiate agonists, including codeine, in the presence of head injury, intracranial lesions, or a pre-existing increase in intracranial pressure. They also may produce adverse reactions such as sedation and pupillary changes which may obscure the clinical course of patients with head injuries.

**Respiratory Conditions with Productive Cough or Chronic Respiratory Disease:** The risks and benefits of opiate agonists or cough suppressants, including codeine, should be carefully considered in illness associated with productive cough or in chronic respiratory disease where interference with ability to clear the tracheobronchial tree of secretions would have a deleterious effect on the patient's respiratory function.

**Information for Patients:** Brontex tablets may cause marked drowsiness or may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. Ambulatory patients should be told to avoid engaging in such activities until it is known that they do not become drowsy or dizzy from Brontex tablets. Pediatric patients should be supervised to avoid potential harm in bike riding or in other hazardous activities.

The concomitant use of alcohol or other central nervous system depressants, including opiate agonists, sedatives, hypnotics, and tranquilizers, may have an additive effect and should be avoided or their dosage reduced. Codeine, like other opiate agonists, may produce orthostatic hypotension in some ambulatory patients. Patients should be cautioned accordingly.

**Drug Interactions:** Caution should be used when taking this product with CNS depressants including alcohol, sedatives, tranquilizers and drugs used for depression, especially monoamine oxidase inhibitors (MAOIs). These combinations may cause greater sedation than is caused by the products used alone.

**Drug/Laboratory Test Interactions:** Guaifenesin has been reported to interfere with clinical laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and urinary vanillylmandelic acid (VMA).

Because opiate agonists may increase biliary tract pressure, with resultant increases in plasma amylase or lipase levels, determination of these enzyme levels may be unreliable for 24 hours after an opiate agonist has been given.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Studies with Brontex tablets in animals to evaluate carcinogenic, mutagenic, or impairment of fertility potential have not been conducted. Studies conducted by the National Toxicology Program with codeine in rats and mice to evaluate its carcinogenic potential are in progress.

#### Pregnancy:

**Teratogenic Effects:** Pregnancy Category C. Animal reproduction studies have not been conducted with Brontex tablets. It is also not known whether Brontex tablets can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Brontex tablets should be given to a pregnant woman only if clearly needed.

Studies with codeine in hamsters and mice to evaluate its developmental toxicity potential have been reported by the National Toxicology Program. Codeine produced a decrease in mean fetal weight in both hamsters and mice, but did not produce structural malformations.

**Nonteratogenic Effects:** Dependence has been reported in newborns whose mothers took opiates regularly during pregnancy. Signs of withdrawal include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. These signs usually disappear during the first few days of life.

#### Patent Pending

© 1995 by Procter & Gamble Pharmaceuticals P&GP C.S. Printed in U.S.A. August 1995

Brontex® (codeine phosphate/guaifenesin) tablets

**Labor and Delivery:** Use should be avoided during labor and delivery. Opiates cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. If the mother received opiates during labor, the newborn should be closely observed for signs of respiratory depression. Resuscitation, and in severe cases, naloxone may be required. Codeine may also prolong labor.

**Nursing Mothers:** Codeine is excreted in breast milk in amounts that are probably insignificant when given at usual therapeutic dose. It is not known whether guaifenesin is excreted in breast milk. Caution should be exercised when Brontex tablets are administered to a nursing mother. The possibility of clinically important amounts of codeine being excreted in breast milk in individuals abusing codeine should be considered.

**Pediatric Use:** Brontex tablets are not recommended for use in pediatric patients below the age of 12 years. Brontex liquid is not recommended for use in pediatric patients below the age of 6 years.

#### ADVERSE REACTIONS:

**Nervous System:** CNS depression, particularly respiratory depression, light-headedness, dizziness, sedation, euphoria, dysphoria, headache, transient hallucination, disorientation, visual disturbances, and convulsions.

**Cardiovascular:** Tachycardia, bradycardia, palpitation, faintness, syncope, orthostatic hypotension (common to opiate agonists), and circulatory depression.

**Gastrointestinal:** Nausea, vomiting, stomach pain, constipation, and biliary tract spasm. Patients with chronic ulcerative colitis may experience increased colonic motility; in patients with acute ulcerative colitis, toxic dilation has been reported.

**Genitourinary:** Oliguria and urinary retention; antidiuretic effect has been reported (common to opiate agonists).

**Allergic:** Infrequent pruritus, urticaria, angioneurotic edema, laryngeal edema, and rare anaphylactic reaction.

**Other:** Flushing of the face, sweating, and weakness.

**DRUG ABUSE AND DEPENDENCE:** Brontex tablets are a Schedule III Controlled Substance. Brontex liquid is a Schedule V controlled substance.

Codeine is known to be subject to abuse; however, the abuse potential of oral codeine is lower than that of most other opiate agonists because of its lower potency at therapeutic doses. However, codeine must be administered only under close supervision to patients with a history of drug abuse or dependence.

Psychological dependence, physical dependence, and tolerance are known to occur with codeine.

#### OVERDOSAGE:

**Signs and Symptoms:** Serious overdose with codeine is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, miosis (mydriasis may occur in terminal necrosis or hypoxia), skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

**Treatment:** The treatment of overdosage should provide symptomatic and supportive care. Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation as necessary. The narcotic antagonist naloxone is a specific antidote against respiratory depression resulting from overdosage or unusual sensitivity to opiate agonists, including codeine. Therefore, an appropriate dose of naloxone hydrochloride (see package insert) may be administered, preferably by the intravenous route, and simultaneously with efforts at respiratory resuscitation. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

If the amount ingested is considered dangerous or excessive, induce vomiting with ipecac syrup unless the patient is convulsing, comatose, or has lost the gag reflex, in which case perform gastric lavage using a large-bore tube. If indicated, follow with activated charcoal and a saline cathartic.

#### DOSEAGE AND ADMINISTRATION:

**Adults and pediatric patients 12 years of age and older:** one tablet every 4 hours.

Brontex tablets are not recommended for pediatric patients under 12 years of age.

**Liquid: Adults and pediatric patients 12 years of age and older:** 4 teaspoonsful every 4 hours. **Pediatric patients 6 to under 12 years of age:** 2 teaspoonsful every 4 hours.

#### HOW SUPPLIED:

Brontex tablets are available as a red, capsule-shaped tablet, embossed "BRONTEX".

NDC 0149-0440-01 bottle of 100.

Brontex liquid is available as NDC 0149-0441-16 1 pint (473 mL) bottle.

Store at controlled room temperature (59°-86°F or 15°-30°C).

CAUTION: Federal law prohibits dispensing without prescription.

Procter & Gamble Pharmaceuticals

Cincinnati, Ohio 45202

May 1995

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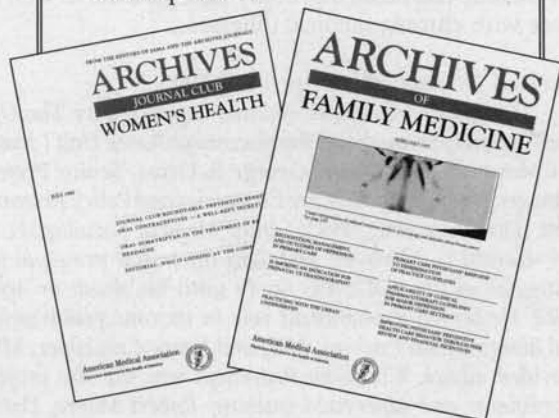
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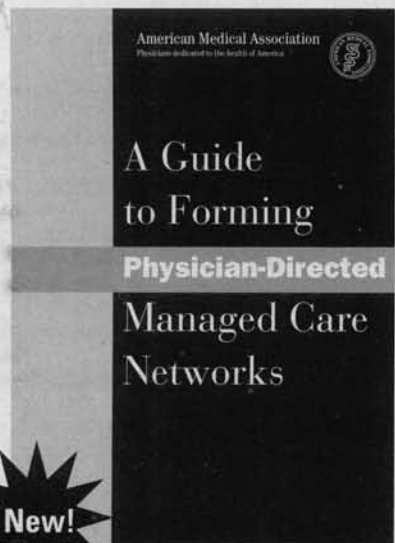


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Please see references and brief summary of prescribing information on adjacent page.

into everyday

# activities

**Relafen® provides potent anti-inflammatory relief of RA and OA with less than 1% incidence of peptic ulcer**

*Relafen* helps patients meet the challenges of everyday tasks by significantly reducing joint pain, morning stiffness, and other symptoms associated with RA and OA.<sup>1-4</sup> And, *Relafen* safely meets the challenges of living with arthritis by minimizing the risk of serious GI damage. In fact, long-term studies lasting up to 2 years indicate *Relafen* has a less than 1% incidence of peptic ulcer.<sup>5</sup>

**Effective relief with a low incidence of peptic ulcer**

**RELAFEN®**  
NABUMETONE

**References** 1. Emery P, Clarke A, Williams P, et al. Nabumetone compared with naproxen in the treatment of rheumatoid arthritis: a multicenter, double blind, randomized, parallel group trial in hospital outpatients. *J Rheumatol*. 1992;19(suppl 36):41-47. 2. Data on file, SmithKline Beecham Pharmaceuticals. 3. Fleischmann RM. Clinical efficacy and safety of nabumetone in rheumatoid arthritis and osteoarthritis. *J Rheumatol*. 1992;19(suppl 36):32-40. 4. Pisko EJ, Bockow BI, Box P, et al. Six-month multi-center study comparing nabumetone with naproxen in the treatment of osteoarthritis. *Am J Med*. 1987;83(suppl 4B):86-91. 5. Relafen® (nabumetone) Prescribing Information.

## RELAFEN®

brand of nabumetone

**Brief Summary:** Consult full prescribing information before using.

**CLINICAL PHARMACOLOGY:** *Relafen* is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic properties in pharmacologic studies. As with other nonsteroidal anti-inflammatory agents, its mode of action is not known. However, the ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect.

The parent compound is a prodrug, which undergoes hepatic biotransformation to the active component, 6-methoxy-2-naphthylacetic acid (6MNA), a potent inhibitor of prostaglandin synthesis.

**INDICATIONS AND USAGE:** Acute and chronic treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis.

**CONTRAINDICATIONS:** Patients (1) who have previously exhibited hypersensitivity to it; (2) in whom *Relafen*, aspirin or other NSAIDs induce asthma, urticaria or other allergic-type reactions.

**WARNINGS:** Remain alert for ulceration and bleeding in patients treated chronically, even in the absence of previous G.I. tract symptoms.

In controlled clinical trials involving 1,677 patients treated with *Relafen* (1,140 followed for one year and 927 for two years), the cumulative incidence of peptic ulcers was 0.3% (95% CI, 0%, 0.6%) at three to six months, 0.5% (95% CI, 0.1%, 0.9%) at one year and 0.8% (95% CI, 0.3%, 1.3%) at two years. Inform patients of the signs and symptoms of serious G.I. toxicity and what steps to take if they occur. In patients with active peptic ulcer, weigh the benefits of *Relafen* therapy against possible hazards, institute an appropriate ulcer treatment regimen and monitor the patients' progress carefully.

In considering the use of relatively large doses (within the recommended dosage range), anticipate benefit sufficient to offset the potential increased risk of G.I. toxicity.

**PRECAUTIONS:** Because nabumetone undergoes extensive hepatic metabolism, no adjustment of *Relafen* dosage is generally necessary in patients with renal insufficiency. However, as with all NSAIDs, monitor patients with impaired renal function more closely than patients with normal renal function.

Evaluate patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, for evidence of the development of a more severe hepatic reaction while on *Relafen* therapy. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue *Relafen*. Use *Relafen* cautiously in patients with severe hepatic impairment.

As with other NSAIDs, use *Relafen* cautiously in patients with a history of congestive heart failure, hypertension or other conditions predisposing to fluid retention.

Based on U.V. light photosensitivity testing, *Relafen* may be associated with more reactions to sun exposure than might be expected based on skin tanning types.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and the physician.

Exercise caution when administering *Relafen* with warfarin since interactions have been seen with other NSAIDs.

In two-year studies conducted in mice and rats, nabumetone had no statistically significant tumorigenic effect. Nabumetone did not show mutagenic potential in the Ames test and mouse micronucleus test *in vivo*. However, nabumetone- and 6MNA-treated lymphocytes in culture showed chromosomal aberrations at 80 mcg/mL and higher concentrations (equal to the average human exposure to *Relafen* at the maximum recommended dose).

Nabumetone did not impair fertility of male or female rats treated orally at doses of 320 mg/kg/day before mating.

**Pregnancy Category C.** Nabumetone did not cause any teratogenic effect in rats given up to 400 mg/kg and in rabbits up to 300 mg/kg orally. However, increased post-implantation loss was observed in rats at 100 mg/kg orally and at higher doses (equal to the average human exposure to 6MNA at the maximum recommended human dose). There are no adequate, well-controlled studies in pregnant women. Use the drug during pregnancy only if clearly needed. Because of the known effect of prostaglandin-synthesis-inhibiting drugs on the human fetal cardiovascular system (closure of ductus arteriosus), use of *Relafen* during the third trimester of pregnancy is not recommended.

The effects of *Relafen* on labor and delivery in women are not known. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats treated throughout pregnancy.

It is not known whether nabumetone or its metabolites are excreted in human milk; however, 6MNA is excreted in the milk of lactating rats. Because of the possible adverse effects of prostaglandin-synthesis-inhibiting drugs on neonates, *Relafen* is not recommended for use in nursing mothers.

Safety and efficacy in children have not been established.

Of the 1,677 patients in U.S. clinical studies who were treated with *Relafen*, 411 patients (24%) were 65 years of age or older; 22 patients (1%) were 75 years of age or older. No overall differences in efficacy or safety were observed between these older patients and younger ones. Similar results were observed in a one-year, non-U.S. postmarketing surveillance study of 10,800 *Relafen* patients, of whom 4,577 patients (42%) were 65 years of age or older.

**ADVERSE REACTIONS: Incidence  $\geq 1\%$ —Probably Causally Related**—Diarrhea (14%), dyspepsia (13%), abdominal pain (12%), constipation\*, flatulence\*, nausea\*, positive stool guaiac\*, dry mouth, gastritis, stomatitis, vomiting, dizziness\*, headache\*, fatigue, increased sweating, insomnia, nervousness, somnolence, pruritus\*, rash\*, tinnitus\*, edema\*.

\*Incidence of reported reaction between 3% and 9%. Reactions occurring in 1% to 3% of the patients are unmarked.

**Incidence  $< 1\%$ —Probably Causally Related**—Anorexia, cholestatic jaundice, duodenal ulcer, dysphagia, gastric ulcer, gastroenteritis, gastrointestinal bleeding, increased appetite, liver function abnormalities, melena, asthenia, agitation, anxiety, confusion, depression, malaise, paresthesia, tremor, vertigo, bullous eruptions, photosensitivity, urticaria, pseudoporphyria cutanea tarda, toxic epidermal necrolysis, vasculitis, weight gain, dyspnea, eosinophilic pneumonia, hypersensitivity pneumonitis, albuminuria, azotemia, hyperuricemia, interstitial nephritis, nephrotic syndrome, vaginal bleeding, abnormal vision, anaphylactoid reaction, anaphylaxis, angioneurotic edema.

**Incidence  $< 1\%$ —Causal Relationship Unknown**—Bilirubinuria, duodenitis, eruption, gallstones, gingivitis, glossitis, pancreatitis, rectal bleeding, nightmares, acne, alopecia, erythema multiforme, Stevens-Johnson Syndrome, angina, arrhythmia, hypertension, myocardial infarction, palpitations, syncope, thrombophlebitis, asthma, cough, dysuria, hematuria, impotence, renal stones, taste disorder, fever, chills, anemia, leukopenia, granulocytopenia, thrombocytopenia, hyperglycemia, hypokalemia, weight loss.

†Adverse reactions reported only in worldwide postmarketing experience or in the literature, not seen in clinical trials, are considered rarer and are italicized.

**OVERDOSAGE:** If acute overdose occurs, empty the stomach by vomiting or lavage and institute general supportive measures as necessary. Activated charcoal, up to 60 grams, may effectively reduce nabumetone absorption. Coadministration of nabumetone with charcoal to man has resulted in an 80% decrease in maximum plasma concentrations of the active metabolite.

One overdose occurred in a 17-year-old female patient who had a history of abdominal pain and was hospitalized for increased abdominal pain following ingestion of 30 *Relafen* tablets (15 grams total). Stools were negative for occult blood and there was no fall in serum hemoglobin concentration. The patient had no other symptoms. She was given an H<sub>2</sub>-receptor antagonist and discharged from the hospital without sequelae.

**DOSE AND ADMINISTRATION:** Recommended starting dose: 1000 mg taken as a single dose with or without food. Some patients may obtain more symptomatic relief from 1500 mg to 2000 mg daily. Dosages over 2000 mg daily have not been studied. Use the lowest effective dose for chronic treatment.

**HOW SUPPLIED: Tablets:** Oval-shaped, film-coated: 500 mg—white, imprinted with the product name RELAFEN and 500, in bottles of 100 and 500, and in Single Unit Packages of 100 (intended for institutional use only); 750 mg—beige, imprinted with the product name RELAFEN and 750, in bottles of 100 and 500, and in Single Unit Packages of 100 (intended for institutional use only).

Store at controlled room temperature (59° to 86°F) in well-closed container; dispense in light-resistant container.

500 mg 100's: NDC 0029-4851-20  
500 mg 500's: NDC 0029-4851-25  
500 mg SUP 100's: NDC 0029-4851-21

750 mg 100's: NDC 0029-4852-20  
750 mg 500's: NDC 0029-4852-25  
750 mg SUP 100's: NDC 0029-4852-21

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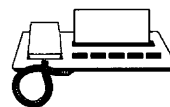
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# ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

R<sub>x</sub>  
Cardizem CD  
Start with one  
180-mg  
capsule daily

## FOR HYPERTENSION OR ANGINA

Brief Summary of  
Prescribing Information as of January 1995

### CARDIZEM® CD (diltiazem HCl) 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

- 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 3290 patients or 0.40%). 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.
- 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 (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
- Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
- 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 (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 of renal and hepatic function 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 Interactions

Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomi-

tantly with other 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. Especially in patients with renal and/or hepatic impairment, dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, may require adjustment when starting or stopping concomitantly administered diltiazem 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%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem. 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 1200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system 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 underdigitalization. (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.

**Cyclosporine.** A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued.

The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

**Carbamazepine.** Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40% to 72% increase), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

##### 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 recom-

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

Adverse Reactions	Cardizem CD (n=607)	Placebo (n=301)
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV Block First Degree	3.3%	0.0%
Edema	2.6%	1.3%
ECG Abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

In clinical trials of CARDIZEM CD capsules, CARDIZEM tablets, and CARDIZEM SR capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%).

In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:

**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, paresis, personality change, somnolence, tinnitus, tremor

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

**Dermatological:** Ptechieae, 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.

Prescribing Information as of January 1995

Marion Merrell Dow Inc.  
Kansas City, MO 64114

ccdb0195c

**References:** 1. Food and Drug Administration. *Approved Drug Products With Therapeutic Equivalence Evaluations* (Orange Book), US Dept of Health and Human Services. 14th ed. Washington, DC; 1994. 2. Cardizem CD prescribing information 3. Data on file, Marion Merrell Dow Inc.



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IN HYPERTENSION OR ANGINA

**CARDIZEM<sup>®</sup> CD**

(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

**FOR EFFECTIVE  
24-HOUR CONTROL**

No other  
diltiazem is  
therapeutically  
equivalent to  
Cardizem CD<sup>1</sup>



**ONCE A DAY**

**A unique hemodynamic and safety profile  
for hypertension or angina<sup>2,3</sup>**

- A side-effect discontinuation rate comparable to placebo in both hypertension and angina trials<sup>3</sup>
- Most commonly reported side effects are headache (5.4%), bradycardia (3.3%), first-degree AV block (3.3%), dizziness (3.0%), edema (2.6%), ECG abnormality (1.6%), and asthenia (1.8%)<sup>2</sup>

Please see brief summary of prescribing information on adjacent page.