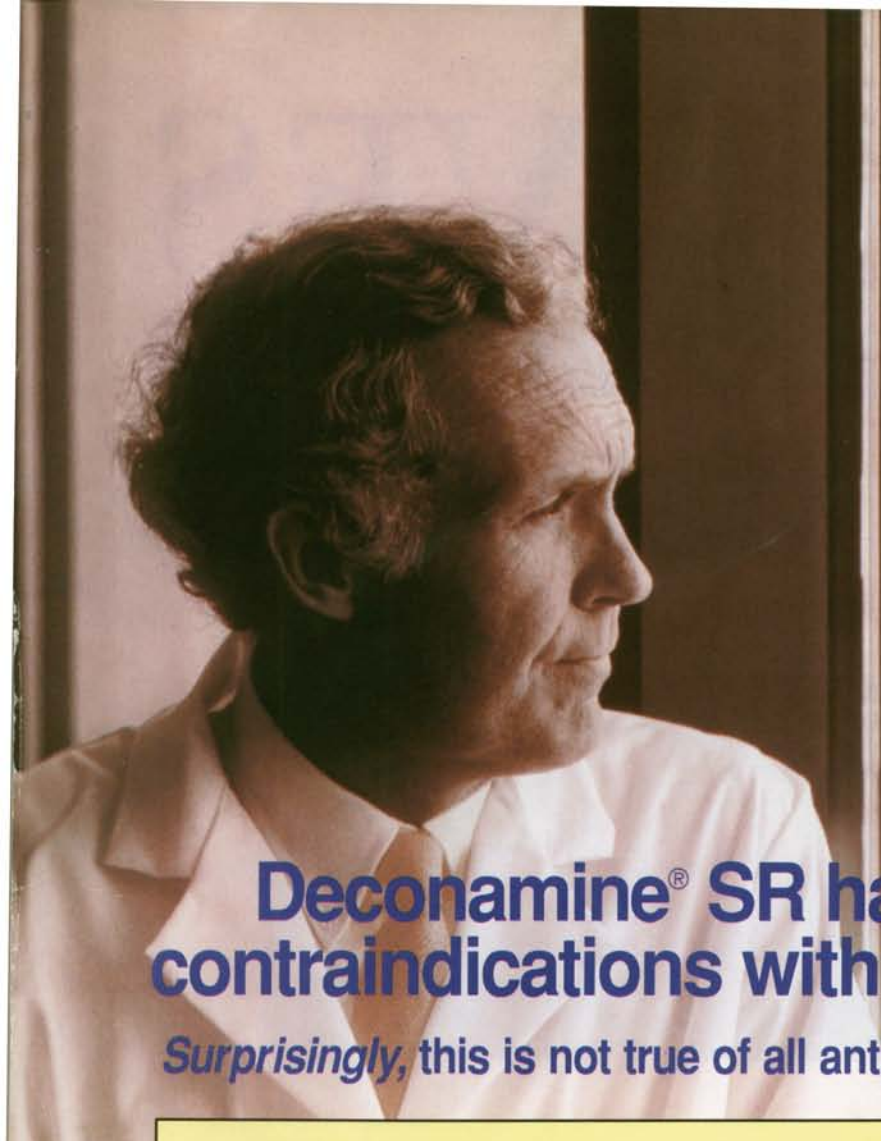

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***Surprisingly,* this is not true of all antihistamine/decongestants.**

Deconamine® SR

(chlorpheniramine maleate, 8 mg /*d*-pseudoephedrine HCl, 120 mg)

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- Mild CNS effect
- Low sedation[1]
- Lowest reported cardiotoxicity profile[2]

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.

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Please see accompanying brief summary of Product Information.

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References:
1. May RJ. Allergic rhinits. *Pharmacotherapy: A Pathophysiologic Approach.* 1989:945-947.
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® 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 methyldopa, reserpine, veratrum alkaloids and mecamylamine.

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

Care should be taken in administering DECONAMINE® 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® medications. It is also not known whether DECONAMINE® medications can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. DECONAMINE® 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® 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.

DOSAGE AND ADMINISTRATION:

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

Tablets: Adults and children over 12 years, 1 tablet three or four times daily. Children under 12 years, DECONAMINE® 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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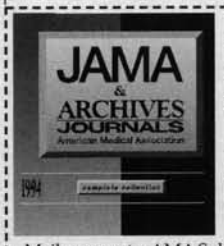

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Ambien® ℞
(zolpidem tartrate)

References: 1. Data on file. Searle. **2.** Vogel G, Scharf M, Walsh J, et al. Effects of chronically administered zolpidem on the sleep of healthy insomniacs. *Sleep Research.* 1989;18:80. Abstract. **3.** Walsh JK, Schweitzer PK, Sugerman JL, et al. Transient insomnia associated with a 3-hour phase advance of sleep time and treatment with zolpidem. *J Clin Psychopharmacol.* 1990;10:184-189.

BRIEF SUMMARY

INDICATIONS AND USAGE

Ambien (zolpidem tartrate) is indicated for the short-term treatment of insomnia. Hypnotics should generally be limited to 7 to 10 days of use, and reevaluation of the patient is recommended if they are to be taken for more than 2 to 3 weeks.

Ambien should not be prescribed in quantities exceeding a 1-month supply (see *Warnings*).

CONTRAINDICATIONS

None known.

WARNINGS

Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness which should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including Ambien. Because some of the important adverse effects of Ambien appear to be dose related (see *Precautions* and *Dosage and Administration*), it is important to use the smallest possible effective dose, especially in the elderly.

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (eg, aggressiveness and extroversion that seemed out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above are drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Following the rapid dose decrease or abrupt discontinuation of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs (see *Drug Abuse and Dependence*).

Ambien, like other sedative/hypnotic drugs, has CNS-depressant effects. Due to the rapid onset of action, Ambien should only be ingested immediately prior to going to bed. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of Ambien. Ambien showed additive effects when combined with alcohol and should not be taken with alcohol. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when Ambien is administered with such agents because of the potentially additive effects.

PRECAUTIONS

General

Use in the elderly and/or debilitated patients: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. Therefore, the recommended Ambien dosage is 5 mg in such patients (see *Dosage and Administration*) to decrease the possibility of side effects. These patients should be closely monitored.

Use in patients with concomitant illness: Clinical experience with Ambien in patients with concomitant systemic illness is limited. Caution is advisable in using Ambien in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Although preliminary studies did not reveal respiratory depressant effects at hypnotic doses of Ambien in normals, precautions should be observed if Ambien is prescribed to patients with compromised respiratory function, since sedative/hypnotics have the capacity to depress respiratory drive. Post-marketing reports of respiratory insufficiency, most of which involved patients with pre-existing respiratory impairment, have been received. Data in end-stage renal failure patients repeatedly treated with Ambien did not demonstrate drug accumulation or alterations in pharmacokinetic parameters. No dosage adjustment in renally impaired patients is required; however, these patients should be closely monitored (see *Pharmacokinetics*). A study in subjects with hepatic impairment did reveal prolonged elimination in this group; therefore, treatment should be initiated with 5 mg in patients with hepatic compromise, and they should be closely monitored.

Use in depression: As with other sedative/hypnotic drugs, Ambien should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

Information for patients: Patient information is printed in the complete prescribing information and is available in pads for distribution to patients.

Laboratory tests: There are no specific laboratory tests recommended.

Drug interactions

CNS-active drugs: Ambien was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs. A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance. The lack of a drug interaction following single-dose administration does not predict a lack following chronic administration.

An additive effect on psychomotor performance between alcohol and zolpidem was demonstrated.

Since the systematic evaluations of Ambien in combination with other CNS-active drugs have been limited, careful consideration should be given to the pharmacology of any CNS-active drug to be used with zolpidem. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of zolpidem.

Other drugs: A study involving cimetidine/zolpidem and ranitidine/zolpidem combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem. Zolpidem had no effect on digoxin kinetics and did not affect prothrombin time when given with warfarin in normal subjects. Zolpidem's sedative/hypnotic effect was reversed by flumazenil; however, no significant alterations in zolpidem pharmacokinetics were found.

Drug/Laboratory test interactions: Zolpidem is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenesis: Zolpidem was administered to rats and mice for 2 years at dietary dosages of 4, 18, and 80 mg/kg/day. In mice, these doses are 26 to 520 times or 2 to 35 times the maximum 10-mg human dose on a mg/kg or mg/m² basis, respectively. In rats these doses are 43 to 876 times or 6 to 115 times the maximum 10-mg human dose on a mg/kg or mg/m² basis, respectively. No evidence of carcinogenic potential was observed in mice. Renal liposarcomas were seen in 4/100 rats (3 males, 1 female) receiving 80 mg/kg/day and a renal lipoma was observed in one male rat at the 18 mg/kg/day dose. Incidence rates of lipoma and liposarcoma for zolpidem were comparable to those seen in historical controls and the tumor findings are thought to be a spontaneous occurrence.

Mutagenesis: Zolpidem did not have mutagenic activity in several tests including the Ames test, genotoxicity in mouse lymphoma cells in vitro, chromosomal aberrations in cultured human lymphocytes, unscheduled DNA synthesis in rat hepatocytes in vitro, and the micronucleus test in mice.

Impairment of fertility: In a rat reproduction study, the high dose (100 mg base/kg) of zolpidem resulted in irregular estrus cycles and prolonged precoital intervals, but there was no effect on male or female fertility after daily oral doses of 4 to 100 mg base/kg or 5 to 130 times the recommended human dose in mg/m². No effects on any other fertility parameters were noted.

Pregnancy

Category B. Studies to assess the effects of zolpidem on human reproduction and development have not been conducted.

Teratology studies were conducted in rats and rabbits.

In rats, adverse maternal and fetal effects occurred at 20 and 100 mg base/kg and included dose-related maternal lethargy and ataxia and a dose-related trend to incomplete ossification of fetal skull bones.

In rabbits, dose-related maternal sedation and decreased weight gain occurred at all doses tested. At the high dose, 16 mg base/kg, there was an increase in postimplantation fetal loss and underossification of sternebrae in viable fetuses.

This drug should be used during pregnancy only if clearly needed.

Nonteratogenic effects: Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. However, children born of mothers taking sedative/hypnotic drugs may be at some risk for withdrawal symptoms from the drug during the postnatal period. In addition, neonatal flaccidity has been reported in infants born of mothers who received sedative/hypnotic drugs during pregnancy.

Labor and delivery: Ambien has no established use in labor and delivery.

Nursing mothers: Studies in lactating mothers indicate that between 0.004 and 0.019% of the total administered dose is excreted into milk, but the effect of zolpidem on the infant is unknown.

The use of Ambien in nursing mothers is not recommended.

Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Associated with discontinuation of treatment: Approximately 4% of 1,701 patients who received zolpidem at all doses (1.25 to 90 mg) in U.S. premarketing clinical trials discontinued treatment because of an adverse clinical event. Events most commonly associated with discontinuation from U.S. trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%), and vomiting (0.5%).

Approximately 6% of 1,320 patients who received zolpidem at all doses (5 to 50 mg) in similar foreign trials discontinued treatment because of an adverse event. Events most commonly associated with discontinuation from these trials were daytime drowsiness (1.6%), amnesia (0.6%), dizziness (0.6%), headache (0.6%), and nausea (0.6%).

Incidence in controlled clinical trials

Most commonly observed adverse events in controlled trials: During short-term treatment (up to 10 nights) with Ambien at doses up to 10 mg, the most commonly observed adverse events associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were drowsiness (reported by 2% of zolpidem patients), dizziness (1%), and diarrhea (1%). During longer-term treatment (28 to 35 nights) with zolpidem at doses up to 10 mg, the most commonly observed adverse events associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were dizziness (5%) and drugged feelings (3%).

Incidence of Treatment-Emergent Adverse Experiences in Short-term Placebo-Controlled Clinical Trials
(Percentage of patients reporting)

Body System/ Adverse Event*	Zolpidem (≤ 10 mg) (N=685)	Placebo (N=473)
Central and Peripheral Nervous System		
Headache	7	6
Drowsiness	2	–
Dizziness	1	–
Gastrointestinal System		
Nausea	2	3
Diarrhea	1	–
Musculoskeletal System		
Myalgia	1	2

*Events reported by at least 1% of Ambien patients are included.

Incidence of Treatment-Emergent Adverse Experiences in Long-term Placebo-Controlled Clinical Trials
(Percentage of patients reporting)

Body System/ Adverse Event*	Zolpidem (≤ 10 mg) (N=152)	Placebo (N=161)
Autonomic Nervous System		
Dry mouth	3	1
Body as a Whole		
Allergy	4	1
Back pain	3	2
Influenza-like symptoms	2	–
Chest pain	1	–
Fatigue	1	2
Cardiovascular System		
Palpitation	2	–
Central and Peripheral Nervous System		
Headache	19	22
Drowsiness	8	5
Dizziness	5	1
Lethargy	3	1
Drugged feeling	3	–
Lightheadedness	2	1
Depression	2	1
Abnormal dreams	1	–
Amnesia	1	–
Anxiety	1	1
Nervousness	1	3
Sleep disorder	1	–
Gastrointestinal System		
Nausea	6	6
Dyspepsia	5	6
Diarrhea	3	2
Abdominal pain	2	2
Constipation	2	1
Anorexia	1	1
Vomiting	1	1
Immunologic System		
Infection	1	1
Musculoskeletal System		
Myalgia	7	7
Arthralgia	4	4

Incidence of Treatment-Emergent Adverse Experiences in Long-term Placebo-Controlled Clinical Trials (Cont'd)
(Percentage of patients reporting)

Body System/ Adverse Event*	Zolpidem (≤ 10 mg) (N=152)	Placebo (N=161)
Respiratory System		
Upper respiratory infection	5	6
Sinusitis	4	2
Pharyngitis	3	1
Rhinitis	1	3
Skin and Appendages		
Rash	2	1
Urogenital System		
Urinary tract infection	2	2

*Events reported by at least 1% of patients treated with Ambien.

There is evidence from dose comparison trials suggesting a dose relationship for many of the adverse events associated with zolpidem use, particularly for certain CNS and gastrointestinal adverse events.

Adverse events are further classified and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 subjects, infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Frequent: abdominal pain, amnesia, ataxia, confusion, depression, diarrhea, diplopia, dizziness, dreaming abnormal, drowsiness, drugged feeling, dry mouth, dyspepsia, euphoria, fatigue, headache, insomnia, lethargy, lightheadedness, myalgia, nausea, upper respiratory infection, vertigo, vision abnormal, vomiting.

Infrequent: agitation, allergy, anorexia, anxiety, arthralgia, arthritis, asthenia, back pain, bronchitis, cerebrovascular disorder, chest pain, constipation, coughing, cystitis, decreased cognition, detached, difficulty concentrating, dysarthria, dysphagia, dyspnea, edema, emotional lability, eye irritation, falling, fever, flatulence, gastroenteritis, hallucination, hiccup, hyperglycemia, hypertension, hypoaesthesia, infection, influenza-like symptoms, malaise, menstrual disorder, migraine, nervousness, pallor, palpitation, paresthesia, pharyngitis, postural hypotension, pruritus, rash, rhinitis, scleritis, SGPT increased, sinusitis, sleep disorder, sleeping (after daytime dosing), stupor, sweating increased, tachycardia, taste perversion, tinnitus, tooth disorder, trauma, tremor, urinary incontinence, urinary tract infection, vaginitis.

Rare: abdominal body sensation, abscess, acne, acute renal failure, aggressive reaction, allergic reaction, allergy aggravated, anaphylactic shock, anemia, appetite increased, arrhythmia, arteritis, arthrosis, bilirubinemia, breast fibroadenosis, breast neoplasm, breast pain female, bronchospasm, bullous eruption, BUN increased, circulatory failure, corneal ulceration, delusion, dementia, depersonalization, dermatitis, dysphasia, dysuria, edema periorbital, enteritis, epistaxis, eructation, esophagospasm, ESR increased, extrasystoles, eye pain, face edema, feeling strange, flushing, furunculosis, gastritis, glaucoma, gout, hemorrhoids, hepatic function abnormal, herpes simplex, herpes zoster, hot flashes, hypercholesteremia, hyperhemoglobinemia, hyperkalemia, hypertension aggravated, hypotension, hypotonia, hypoxia, hysteria, illusion, impotence, injection site inflammation, intestinal obstruction, intoxicated feeling, lacrimation abnormal, laryngitis, leg cramps, leukopenia, libido decreased, lymphadenopathy, macrocytic anemia, manic reaction, micturition frequency, muscle weakness, myocardial infarction, neuralgia, neuritis, neuropathy, neurosis, otitis externa, otitis media, pain, panic attack, paresis, personality disorder, phlebitis, photopsia, photosensitivity reaction, pneumonia, polyuria, pulmonary edema, pulmonary embolism, purpura, pyelonephritis, rectal hemorrhage, renal pain, restless legs, rigors, saliva altered, sciatica, SGOT increased, somnambulism, suicide attempt, syncope, tendinitis, tenesmus, tetany, thinking abnormal, thirst, tolerance increased, tooth caries, urinary retention, urticaria, varicose veins, ventricular tachycardia, weight decrease, yawning.

DRUG ABUSE AND DEPENDENCE

Controlled substance: Schedule IV.

Abuse and dependence: Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem tartrate 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg was difficult to distinguish from placebo.

Sedative/hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. These reported symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The U.S. clinical trial experience from zolpidem does not reveal any clear evidence for withdrawal syndrome. Nevertheless, the following adverse events included in DSM-III-R criteria for uncomplicated sedative/hypnotic withdrawal were reported at an incidence of ≤ 1% during U.S. clinical trials following placebo substitution occurring within 48 hours following last zolpidem treatment: fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal discomfort.

Individuals with a history of addiction to, or abuse of, drugs or alcohol are at risk of habituation and dependence; they should be under careful surveillance when receiving any hypnotic.

OVERDOSAGE

Signs and symptoms: In European postmarketing reports of overdose with zolpidem alone, impairment of consciousness has ranged from somnolence to light coma, with one case each of cardiovascular and respiratory compromise. Individuals have fully recovered from zolpidem tartrate overdoses up to 400 mg (40 times the maximum recommended dose). Overdose cases involving multiple CNS-depressant agents, including zolpidem, have resulted in more severe symptomatology, including fatal outcomes.

Recommended treatment: General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenil may be useful. Respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Sedating drugs should be withheld following zolpidem overdosage. Zolpidem is not dialyzable.

The possibility of multiple drug ingestion should be considered.

Caution: Federal law prohibits dispensing without prescription.

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Awakenings were reduced, compared to placebo.

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First in a unique chemical class of non-benzodiazepine sleep agents

Please see references and brief summary of prescribing information on the last page of this advertisement.

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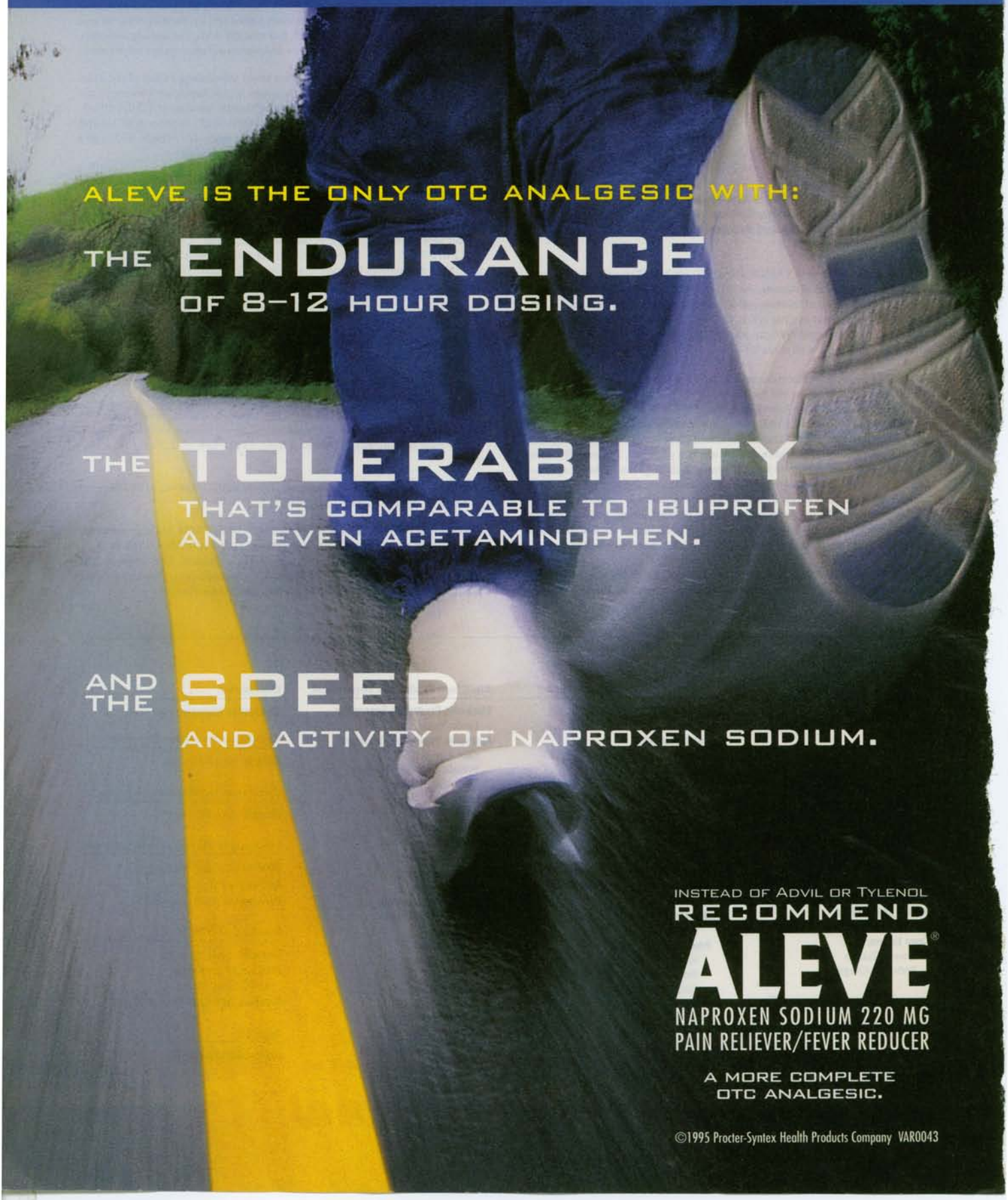

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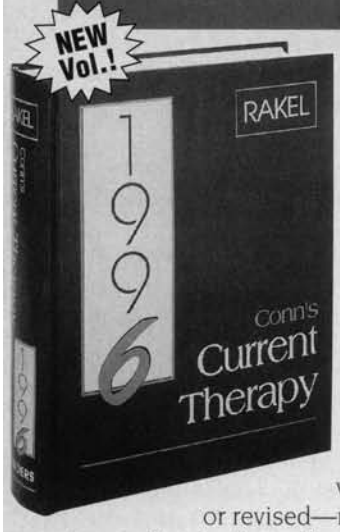

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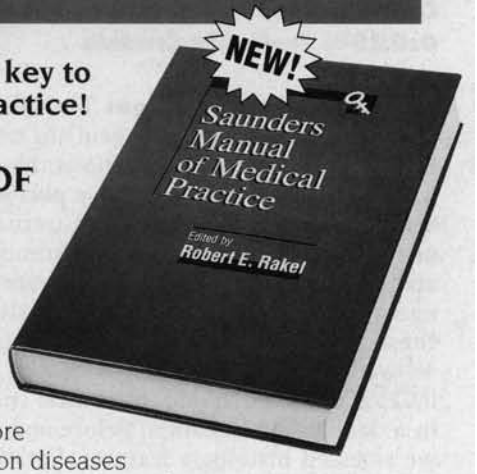

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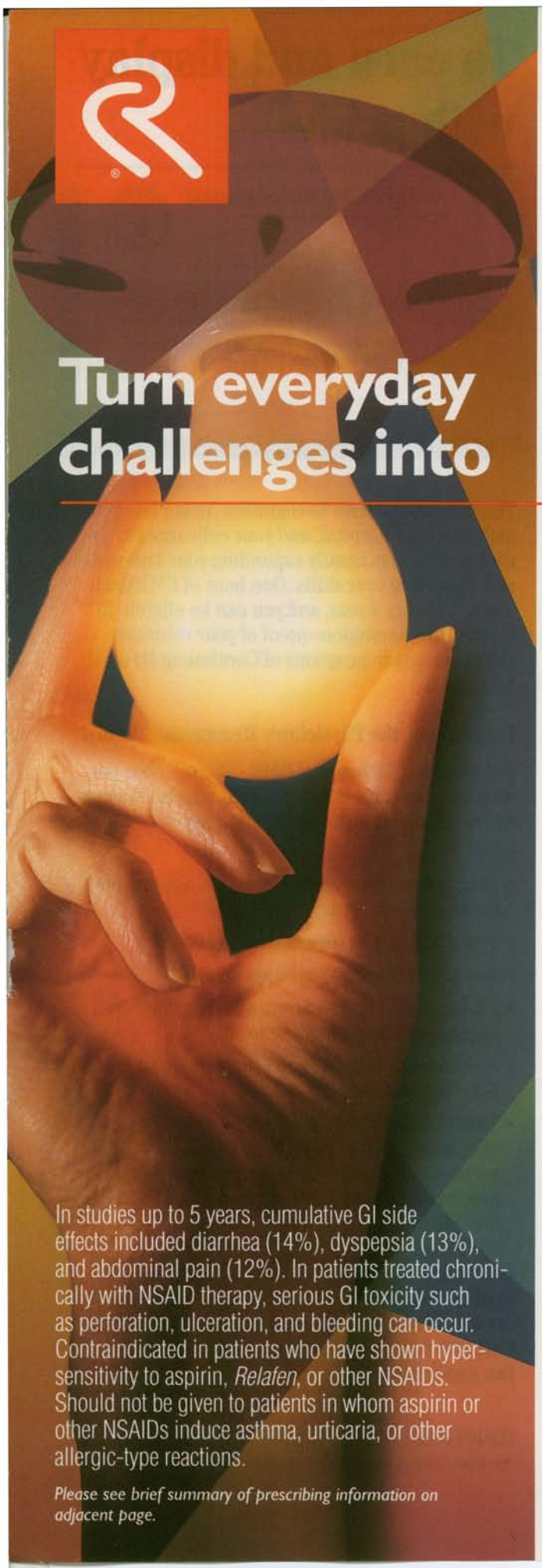

Turn everyday challenges into everyday *activities*

In studies up to 5 years, cumulative GI side effects included diarrhea (14%), dyspepsia (13%), and abdominal pain (12%). In patients treated chronically with NSAID therapy, serious GI toxicity such as perforation, ulceration, and bleeding can occur. Contraindicated in patients who have shown hypersensitivity to aspirin, *Relafen*, or other NSAIDs. Should not be given to patients in whom aspirin or other NSAIDs induce asthma, urticaria, or other allergic-type reactions.

Please see brief summary of prescribing information on adjacent page.

Effective relief with a low incidence of peptic ulcer

RELAFEN®
nabumetone

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 ≥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, eructation, 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_2-receptor antagonist and discharged from the hospital without sequelae.

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

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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).[1] 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®

CODEINE PHOSPHATE...10mg
(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 teaspoonfuls (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 in patients with known hypersensitivity to any of its ingredients. **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.

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.

DOSAGE 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 teaspoonfuls every 4 hours. **Pediatric patients 6 to under 12 years of age:** 2 teaspoonfuls 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.
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National Health Council December Events

What?

December 13: The National Health Council's 75th Anniversary Gala Reception

December 14: The 42nd National Health Forum

Where?

Hyatt Regency Capitol Hill, Washington, DC

When?

December 13: Diamond Anniversary Gala Reception 5:30–7:30 pm

December 14: 42nd National Health Forum on "Quality Managed Care: Meeting the Needs of High-Risk Patients and Populations"—8:45 am until 5:00 pm

Who?

Shakers and Movers in Health Care (President and Mrs. Clinton have been invited, along with key members of the Cabinet, leaders and key staff in the Congress, members of all Council Member organizations, and selected guests from the private and public sectors)

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National Health Council
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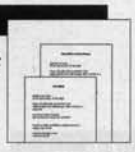

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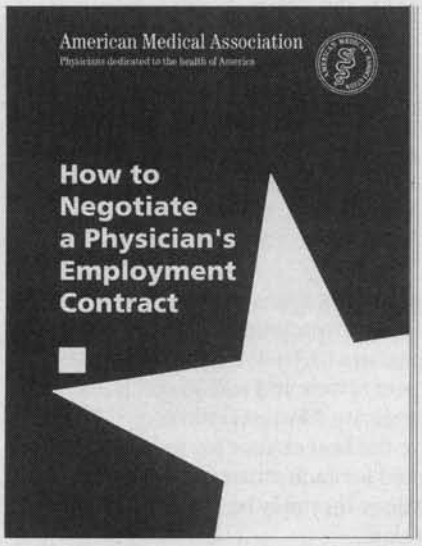

Most suits brought by medical entities for breach of contract allege violation of covenants not to compete, also known as restrictive covenants. Physicians entering their first employment following residency training too often anticipate a permanent career relationship and sign contracts containing restrictive covenants. These may result in a severe economic hardship for the physician if the physician is forced to relocate after a brief period of employment.

How to Negotiate a Physician's Employment Contract, just published by the American Medical Association (AMA), provides an extensive review of cases involving judicial treatment of restrictive covenants and numerous other issues physicians and employers need to know before signing an employment contract. These include compensation, essential information about the Americans with Disabilities Act, impact of income taxes on various forms of compensation and an overview of the Stark II self-referral legislation.

A basic specimen form of a physician's employment agreement, a checklist for preparing an employment contract and an array of optional and alternative clauses are also included.

Written for both employers and physicians, this new publication offers a road map for exploring every critical aspect of a contract and for paving the way to a satisfactory relationship between employer and employee. Published June, 1995. 43 pages.

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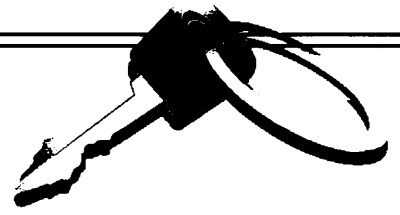

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Over the past 15 years, eight large controlled clinical trials of antihypertensive therapy in the elderly have clearly documented that treatment is associated with a reduction in the incidence of strokes. The meta-analysis of these data reported in the article by Pearce et al clearly demonstrates a reduction of 18% in the incidence of coronary heart disease, a 35% reduction in the incidence of strokes, and a significant reduction in mortality rate, along with a blood pressure reduction of 15/6 mm Hg (systolic/diastolic) over approximately a 5-year period. Further analysis of these results suggests that diuretics and β-blockers were equally efficacious for stroke prevention, but diuretics may be superior in terms of reducing coronary heart disease events and the all-cause mortality rate.

The results of this meta-analysis as well as those of the Systolic Hypertension in the Elderly Program and the Medical Research Council Hypertension Trial support the concept that the practioner should be more aggressive in lowering blood pressure in the geriatric population. Furthermore, the treatment of systolic hypertension, which is relatively common in this population, is as important, if not more critical, in the treatment of diastolic hypertension.

Based on the available data, it appears that therapy with low-dose diuretics (25 mg or less of hydrochlorothiazide) should be the cornerstone of therapy for both systolic and diastolic hypertension in the elderly. Indeed, low-dose diuretic therapy is generally well tolerated and does not cause clinically relevant metabolic problems in this population. In contrast to negative notions held in the past regarding compliance and tolerance issues in antihypertensive therapy, we now know that compliance is at least as good as it is in younger individuals. Thus, we have relatively inexpensive, generally well tolerated antihypertensive medications that have been proven to reduce the incidence of stroke and coronary events and the all-cause mortality rate. Unfortunately, this information has not been adequately conveyed to many practitioners who still do not appreciate the tremendous benefits of treating elevated blood pressures in the most rapidly growing patient population in the United States and other Westernized countries: the elderly.

James R. Sowers, MD
Wayne State University School of Medicine
Detroit, Mich

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Correspondence to Institute for Research in Extramural Medicine, Vrije Universiteit Amsterdam, Van der Boechorststraat 7, 1081 BT Amsterdam, the Netherlands (Dr Onwuteaka-Philipsen).

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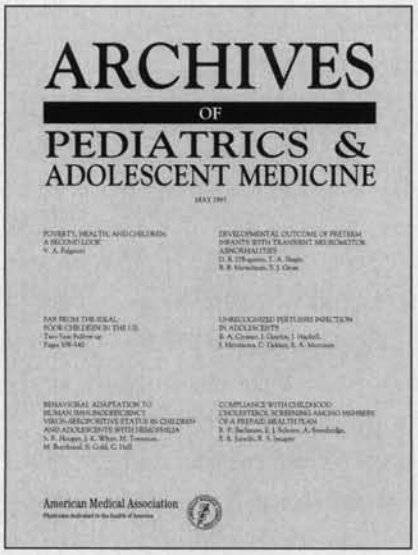

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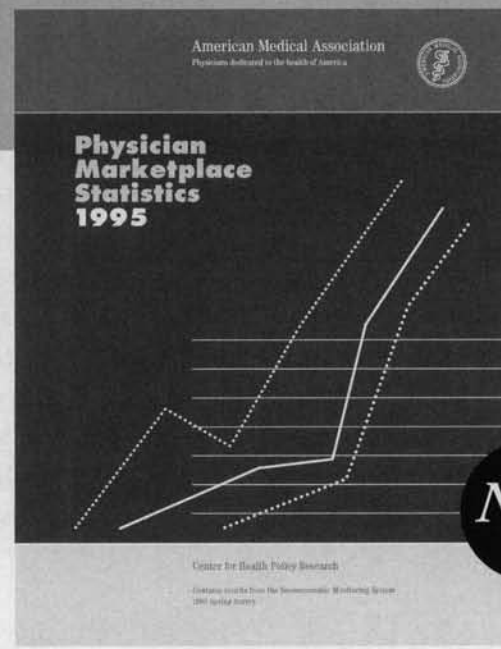

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(BRCA2), located at 13q12-13, may be responsible for some inherited breast cancers, and that p53 mutations and the ataxia telangiectasia gene may also cause breast cancer.

Conclusion: Important further questions are raised by this discovery, ie, what are the biologic functions of the gene product; are there other genes located on chromosome 17q that play a role in sporadic breast cancer; are there other genes elsewhere causing susceptibility to breast cancer? The importance of this discovery is made clear not only by the significant contribution it makes to understanding cancer biology but also by the high prevalence of breast cancer.

Reprint Requests: The Johns Hopkins Oncology Center, Baltimore, MD 21231 (B. Vogelstein).

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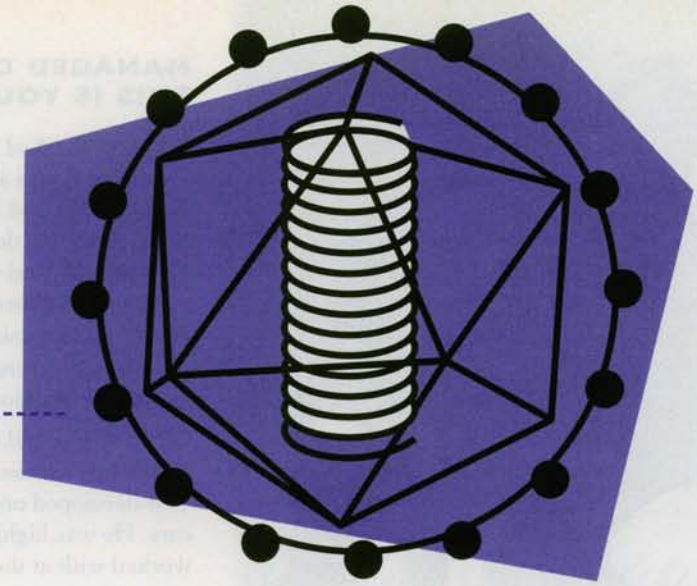

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CARDIZEM® CD

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

FOR HYPERTENSION OR ANGINA

℞ *Cardizem CD Start with one 180-mg capsule daily*

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

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 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.
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 (diltiazem hydrochloride) 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 (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 concomitantly 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 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.

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 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 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.

CARDIZEM CD Capsule Placebo-Controlled Angina and Hypertension Trials Combined

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, paresthesia, 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: 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.

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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ONCE A DAY

A unique hemodynamic and safety profile for hypertension or angina[2,3]

- A side-effect discontinuation rate comparable to placebo in both hypertension and angina trials[3]
- 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%)[2]

Please see brief summary of prescribing information on adjacent page.