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John L. Orchard, MD; John Stramat, MD; Marie Wolfgang, MD; Amanda Trimpey

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hemoglobin was significantly associated with mortality from diabetes (HR, 1.32; 95% CI, 1.21 to 1.43), ischemic heart disease (HR, 1.10; 95% CI, 1.04 to 1.17), and stroke (HR, 1.17; 95% CI, 1.05 to 1.30), but not cancer (HR, 0.99; 95% CI, 0.88 to 1.10). Results for any mention of specific causes of death were similar.

**Conclusion:** These results suggest possible benefit to the control of glycaemia with respect to death due to vascular disease and diabetes.


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**ARCHIVES OF NEUROLOGY**

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**Pregnancy and Multiple Sclerosis: A Prospective Study**

**Objective:** To conduct a prospective assessment of pregnancy on women with multiple sclerosis (MS), focusing on pregnancy outcome and relapses during gestation and up to 6 months after delivery.

**Design:** Expected numbers of relapses were based on data for (1) “self-controls”: the mothers (“cases”) themselves prior to becoming pregnant and (2) “matched controls”: female patients with MS “matched” to the mothers for year of birth, age of MS onset, MS type, MS course, and initial MS symptom(s).

**Setting:** Cases and controls were identified from an ambulatory care MS clinic that serves the province of British Columbia, Canada.

**Patients or Other Participants:** Women with a diagnosis of MS who attended the MS clinic during 1982 through 1986 and subsequently became pregnant during 1982 through 1989 inclusive were included in the study as cases. Matched controls were women with MS who attended the MS clinic during the same period but did not become pregnant.

**Results:** No significant increase in relapse rate was found for cases during the first two trimesters of gestation. The number of relapses was significantly less than expected during the third trimester compared with matched controls ($\chi^2=6.80, df=1, P<.02$), but not compared with self-controls ($\chi^2=3.39, df=1, P>.05$). The observed number of relapses for the 6 months after delivery did not differ significantly from expected (self-controls: $\chi^2=2.84, df=2, P>.05$; matched controls: $\chi^2=1.76, df=2, P>.05$).

**Conclusion:** These data suggest that neither pregnancy nor the 6-month period after delivery is a risk factor for relapse in MS. They are consistent with previous observations that, in the long term, pregnancy does not influence subsequent MS disability.

(1994;51:1120-1124) A. Dezza Sadovnik, PhD, et al, Department of Medical Genetics, University of British Columbia, Room 226, 6174 University Blvd, Vancouver, British Columbia, Canada V6T 1Z3.
Turn everyday challenges into everyday activities

*GI symptoms comparable to other NSAIDs, including diarrhea, dyspepsia, and abdominal pain. In patients treated chronically with NSAID therapy, serious GI toxicity such as perforation, ulceration, and bleeding can occur.

As with other NSAIDs, rare renal and hepatic reactions have been reported. Please see precautions section of prescribing information. Contraindicated in patients who are hypersensitive to aspirin or other NSAIDs.

Please see brief summary of prescribing information on adjacent page.

Effective relief with a low incidence of peptic ulcer*
RELAFEN
brand of nabumetone

Brief Summary: This product is a nonprescription medication.

CLINICAL PHARMACOLOGY: RELAFEN is a nonsteroidal anti-inflammatory drug (NSAID) that is a member of the indomethacin class of drugs. Relafen is used for the treatment of mild to moderate pain and inflammation.

INDICATIONS AND USAGE: Relafen is indicated for the treatment of mild to moderate pain and inflammation associated with acute musculoskeletal conditions, such as arthritis.

CONTRAINDICATIONS: Patients with a history of hypersensitivity to nabumetone should not use this medication.

WARNINGS: Use in pregnancy: Relafen is not recommended for use in pregnant women.

PRECAUTIONS: Use in children: The safety and efficacy of Relafen in children have not been established.

ADVERSE REACTIONS: The most common adverse reactions reported with Relafen use include gastrointestinal disturbances, such as nausea and vomiting.

DOSE AND ADMINISTRATION: The recommended dose for adults is one tablet (500 mg) taken orally every 8 hours, as needed.

HOW SUPPLIED: Tablets: Each tablet contains 500 mg of nabumetone.

STORAGE: Store at controlled room temperature (15° to 30°C) in well-closed containers.

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Cough relief designed to make remaining coughs more productive. Now, help relieve dry, hacking coughs and make the most of remaining coughs with new Brontex—the codeine formula with the most guaifenesin.

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Only new Brontex combines 10 mg codeine—the most commonly prescribed level of the antitussive many doctors prefer—with 300 mg guaifenesin—the expectorant with the time-proven safety profile—in a convenient, single-tablet dose.

Only Brontex exceeds the minimum therapeutic requirements for guaifenesin. Unlike other codeine brands, new Brontex, with its convenient dosing regimen, reaches well into the daily therapeutic range for guaifenesin (1,200 mg to 2,400 mg) set by federal guidelines.

Now for dry, unproductive coughs, there’s new Brontex—the codeine cough formula with the most guaifenesin.

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CODEINE PHOSPHATE...10mg
(Warning: May be habit forming)

GUAIFENESIN ..........300mg

FEWER COUGHS, WETTER COUGHS

Please see brief summary of prescribing information on next page.
Cough relief designed to make remaining coughs more productive

Up to 3 times more guaifenesin than other codeine brands

Exceeds the minimum therapeutic requirements for guaifenesin set by federal guidelines

Fewer Coughs, Wetter Coughs

Codeine may cause sedation and have additive sedative effects with other CNS depressants.*

Brontex (codeine phosphate/guaifenesin) tablets

DESCRIPTION: Each Brontex tablet and 4 teaspoonfuls (20 mL) of Brontex liquid contains codeine phosphate 10 mg and guaifenesin 300 mg.

Indications and Usage: Temporarily relieves cough due to minor throat and bronchial irritation as may occur with a cold, or inflamed linens. Helps loosen phlegm (mucus) and thin bronchial secretions to help bronchial passages 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 children under 2 years of age. Guaifenesin is not recommended for use in children under 12 years of age. Guaifenesin is not recommended for use in children under 12 years of age. Codeine may cause sedation and have additive sedative effects with other CNS depressants. Codeine may cause sedation and have additive sedative effects with other CNS depressants. Codeine may cause sedation and have additive sedative effects with other CNS depressants. Codeine may cause sedation and have additive sedative effects with other CNS depressants.

WARNINGS: Codeine is not recommended for use in children under 2 years of age. Children under 12 years of age may be more susceptible to the respiratory depressant effects of codeine, including respiratory arrest, coma, and death. Precautions: General: Codeine should be used with caution in patients with severe COPD, respiratory depression, ophthalmic disorders, or those prone to respiratory depression from respiratory depression, hyperalgesia, or drug addiction. Codeine should be administered with caution to patients with recent abdominal surgery, CNS disorders, seizures, or with a history of drug or alcohol abuse. Adenoids, tonsils, or adenoidectomy have been reported with codeine use.

Hypersensitivity Effects: Codeine may produce hypersensitivity in ambulatory patients.

Overdose: Immediate and Increased Intracranial Pressure: The risk of respiratory depression and elevation of cerebral spinal fluid pressure is increased by opioid agonists, including codeine, in the presence of head injury, intracranial lesions, or a previous increase in intracranial pressure. Caution should be used in patients with a history of any respiratory depression. Increased intracranial pressure should be used in patients with a history of any respiratory depression. Increased intracranial pressure should be used in patients with a history of any respiratory depression.

Respiratory Conditions with Productive Cough or Chronic Respiratory Disease: The risks and benefits of opioid agonists or cough suppressants, including codeine, should be considered in patients with chronic obstructive pulmonary disease or in patients with chronic obstructive pulmonary disease. Use caution in patients with chronic obstructive pulmonary disease. Use caution in patients with chronic obstructive pulmonary disease. Use caution in patients with chronic obstructive pulmonary disease.

Information for Patients: Brontex tablets may cause a change in bowel habits 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. Children should be supervised to prevent potential harm to children in other or in other hazardous activities. The concurrent use of alcohol or other central nervous system depressants, including opiates, sedatives, hypnotics, and tranquillizers, may have an additive effect and should be avoided or their dosage reduced. Codeine, like other opioid agonists, may produce oropharyngeal hypersensitivity in some ambulatory patients. Patients should be counseled accordingly.

Drug Interactions: Codeine should be used when taking this product with CNS depressants including alcohol, sedatives, tranquilizers, or drugs used for depression, especially monoamine oxidase inhibitors (MAOIs). These combinations may cause severe respiratory depression as 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 vanillymandelic acid (VMA). Because of these enzyme inhibitors, the results of these enzyme determinations may be misleading for 24 hours or for 24 hours after an acute dose of guaifenesin 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 not known whether Brontex tablets can cause fetal harm when administered to a pregnant woman or if codeine 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 codeine regularly during pregnancy. Signs of withdrawal include irritability, excessive crying, tremors, hyperactivity, fever, vomiting, and diarrhea. These signs usually disappear during the first few days of life.

Adverse Reactions: Nervous System: CNS depression, particularly respiratory depression, dizziness, drowsiness, sedation, somnolence, paresthesia, headache, facial numbness, dizziness, drowsiness, sedation, somnolence, paresthesia, headache, facial numbness, dizziness, or other adverse reactions to Brontex tablets, should be reported. Guaifenesin may cause sedation and have additive sedative effects with other CNS depressants. Guaifenesin may cause sedation and have additive sedative effects with other CNS depressants. Guaifenesin may cause sedation and have additive sedative effects with other CNS depressants.

Gastrointestinal: Nausea, vomiting, stomach pain, constipation, and biliary tract spasm. Patients with chronic obstructive conditions may experience increased colonic motility; in patients with acute ulcerative colitis, chronic diarrhea is a contraindication. For patients with chronic obstructive conditions may experience increased colonic motility; in patients with acute ulcerative colitis, chronic diarrhea is a contraindication. For patients with chronic obstructive conditions may experience increased colonic motility; in patients with acute ulcerative colitis, chronic diarrhea is a contraindication.

Drug Abuse and Dependence: Brontex tablets are schedule III controlled substances. Codeine is a schedule II controlled substance. Brontex tablets are schedule III controlled substances. Codeine is a schedule II controlled substance. Brontex tablets are schedule III controlled substances. Codeine is a schedule II controlled substance. Brontex tablets are schedule III controlled substances. Codeine is a schedule II controlled substance.

Drug Overdose: Signs and Symptoms: Serious overdose with codeine is characterized by respiratory depression, hypotension, and/or mental or physical signs of overdose, such as a decrease in amplitude and rate of respirations. The median lethal dose in mice is 150 mg/kg body weight. Symptoms of overdose include respiratory depression, hypotension, and/or mental or physical signs of overdose, such as a decrease in amplitude and rate of respirations. The median lethal dose in mice is 150 mg/kg body weight. Symptoms of overdose include respiratory depression, hypotension, and/or mental or physical signs of overdose, such as a decrease in amplitude and rate of respirations. The median lethal dose in mice is 150 mg/kg body weight.

Dosage and Administration: Adults and children 12 years of age and older: one tablet every 4 hours. Brontex tablets are available in 10 mg, 15 mg, and 30 mg tablets. Brontex tablets are available in 10 mg, 15 mg, and 30 mg tablets. Brontex tablets are available in 10 mg, 15 mg, and 30 mg tablets.

HOW SUPPLIED: Brontex tablets are available in 10 mg, 15 mg, and 30 mg tablets. Brontex tablets are available in 10 mg, 15 mg, and 30 mg tablets. Brontex tablets are available in 10 mg, 15 mg, and 30 mg tablets.

CAUTION: Federal law prohibits dispensing without prescription.

*Recommended dosage for most codeine guaifenesin products is two tablets every four hours.

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Brief Summary of Prescribing Information as of April 1993

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

FOR HYPERTENSION OR ANGINA

Cardiovascular Disease, Malnutrition, Impairment of Fertility
A 24-month study in rats of oral dosage levels of up to 100 mg/kg/day and a 21-month study in mice is 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
Cardiovascular Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from full to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal resorptions. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

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

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

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

ADVERSE REACTIONS
Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired venous 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 per day in placebo patients shown for comparison:

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Cardizem CD (n=620)</th>
<th>Placebo (n=301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5.4%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5.0%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>3.3%</td>
<td>1.3%</td>
</tr>
<tr>
<td>AV Block First Degree</td>
<td>3.3%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Edema</td>
<td>2.6%</td>
<td>1.3%</td>
</tr>
<tr>
<td>ECG Abnormality</td>
<td>1.6%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1.6%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

In clinical trials of CARDIZEM CD capsules, CARDIZEM tablets, and CARDIZEM SR capsules involving over 3200 patients, the most common events (i.e., greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.9%), 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, electrocardiogram abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

- Nervous System: Abnormal dreams, amnesia, depression, panic attacks, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tremor.

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

- Dermatological: Pustules, photosensitivity, pruritus, urticaria.

- Other: Antidromy, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, irregular heartbeat, joint pain, knee pain, loss of hand function, nasal congestion, neck pain, leg 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 blood pressure, 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 lichenoid, 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 April 1993
Marion Merrell Dow Inc.
Kansas City, MO 64114
csmh94521

IN HYPERTENSION OR ANGINA

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

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ONCE A DAY

A unique hemodynamic and safety profile for hypertension or angina\(^{1,2}\)

- A side-effect discontinuation rate comparable to placebo in both hypertension and angina trials\(^2\)
- 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%)\(^1\)

Please see brief summary of prescribing information on adjacent page.