"Just one pill, it was so easy."

"I didn't have to deal with any of the mess."

"I like that you can take it anytime."

"I felt better the first day, and great the second."

---

1 Two open-label, multicenter, randomized trials comparing a single oral Diflucan tablet (150 mg) with either 2% miconazole cream (100 mg) once nightly for 7 days or clotrimazole vaginal tablets (100 mg) once nightly for 7 days in 870 women with vaginal yeast infection due to Candida. Clinical cure: complete resolution of signs and symptoms present at the initial assessment; mycologic cure: negative results from both vaginal fungal culture and KOH preparation.

2 Results of two open, multicenter studies of single-dose Diflucan (150 mg) in 188 and 180 women, respectively, with vaginal yeast infections. Patients responding to treatment were asked to estimate times from start of therapy to onset of relief and to complete relief.

§ Wholesale acquisition cost (WAC) provided by Medi-Span®, July 1994. WAC may not necessarily reflect actual pharmacy or out-of-pocket costs. In studies of Diflucan, the clinical and mycologic cure rates in the fluconazole group were comparable with those of the vaginal product group (clotrimazole and miconazole). WAC includes Gyne-Lotrimin® (a registered trademark of Schering-Plough Corp), and Terazol® and Monistat® 7 (both registered trademarks of Ortho Pharmaceutical Corp).

Please see brief summary of prescribing information on last page of this advertisement.
THE ONLY ORAL ONE-DOSE CURE FOR MOST VAGINAL YEAST* INFECTIONS

GREAT NEWS FOR WOMEN IS HERE

Clinical and mycologic cure comparable with 7-day topicals in two separate trials—
One oral Diflucan 150-mg tablet has been shown to be as effective as
7 nights of 2% miconazole cream (100 mg) or 7 nights of clotrimazole
vaginal tablets (100 mg).††

Early symptom relief—In two additional studies of 368 women taking Diflucan,
median time to start of symptom relief was 1 day (range: 0.04 to 10 days)
and 2 days (range: 0.5 to 20 days) to complete relief.†††

Patients may require reevaluation should symptoms not improve within
3 to 5 days.

Established safety experience—More than 9 million patient days of therapy at the
150-mg dose worldwide. In US clinical trials with 870 women, the most
common side effects with Diflucan were headache (13%), nausea (7%), and
abdominal pain (6%).†

Patients respond to one-dose oral convenience
Easy to take—Diflucan can be taken anytime, anywhere, day or night, with
or without food.†

Less expensive—Diflucan provides full-course therapy that costs less than
leading prescription and most OTC products.††

*Due to Candida

NEW INDICATION

Diflucan®
(fluconazole 150-mg tablet)

THE EASY ORAL CURE
Prothrombin time may be increased in patients receiving concomitant DIFLUCAN and coumarin-type anticoagulants. Careful monitoring of prothrombin time in patients receiving DIFLUCAN and coumarin-type anticoagulants is recommended.

DIFLUCAN increases the plasma concentrations of phenytoin. Careful monitoring of phenytoin concentrations in patients receiving DIFLUCAN and phenytoin is recommended.

DIFLUCAN may significantly increase cyclosporine levels in renal transplant patients with or without renal impairment. Careful monitoring of cyclosporine concentrations and serum creatinine is recommended in patients receiving DIFLUCAN and cyclosporine.

Rifampin enhances the metabolism of concurrently administered DIFLUCAN. Depending on clinical circumstances, consideration should be given to increasing the dose of DIFLUCAN when it is administered with rifampin.

DIFLUCAN increased the serum concentrations of theophylline. Careful monitoring of serum theophylline concentrations in patients receiving DIFLUCAN and theophylline is recommended.

Because of the occurrence of serious cardiac dysrhythmias in patients receiving other azole antifungals in conjunction with terfenadine, an interaction study has been performed, and failed to demonstrate a clinically significant drug interaction. Although these events were not observed in patients receiving DIFLUCAN, the co-administration of DIFLUCAN and terfenadine should be carefully monitored.

Fluconazole tablets coadministered with ethinyl estradiol- and levonorgestrel-containing oral contraceptives produced an overall mean increase in ethinyl estradiol and levonorgestrel levels; however, in some patients there were increases up to 47% and 33% of ethinyl estradiol and levonorgestrel levels. The data presently available indicate that the decreases in some individual ethinyl estradiol and levonorgestrel AUC values with fluconazole treatment are likely the result of random variation. While there is evidence that fluconazole can inhibit the metabolism of ethinyl estradiol and levonorgestrel, there is no evidence that fluconazole is a net inducer of ethinyl estradiol or levonorgestrel metabolism. The clinical significance of these effects is presently unknown.

Physicians should be aware that interaction studies with medications other than those listed in the Clinical Pharmacology section have not been conducted, but such interactions may occur.

Cardiogenic, Myocardial and Importance of Fertility
Fluconazole showed no evidence of cardiogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5 or 10 mg/kg/day (approximately 2-7x the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of S. typhimurium, and in the mouse lymphoma (L5178Y) tk assay. Cytogenetic studies in vitro (marine bone marrow cells, following oral administration of fluconazole) and in vivo (human lymphocytes exposed to fluconazole at 1000 μg/ml) showed no evidence of chromosomal mutations.

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 25, or 50 mg/kg, or with parental doses of 5, 25, or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg p.o. An intravenous perinatal study in rats at 5, 20 and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg (approximately 5-fold the recommended human dose) and 40 mg/kg, but not at 5 mg/kg. The dystocia and parturition were reflected in a slight increase in the number of still-born pups, and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific estrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

Pregnancy
Teratogenic Effects. Pregnancy Category C: Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies, at 5, 10 and 20 mg/kg, and at 5, 25, and 75 mg/kg, respectively. Maternal weight gain was impaired at all dose levels, and abortions occurred at 75 mg/kg (approximately 20-60x the recommended human dose) and 50 and 10 mg/kg higher doses. At doses ranging from 80 mg/kg (approximately 20-60x the recommended human dose) to 300 mg/kg embryolethality in rats was increased and fetal abnormalities included wire ribs, clef palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of unknown effects of lowered estrogen on pregnancy, organogenesis and parturition. There are no adequate and well controlled studies in pregnant women. DIFLUCAN should be used in pregnancy only if the potential benefit justifies the possible risk to the fetus.

Nursing Mothers
Fluconazole is secreted in human milk at concentrations similar to plasma. Therefore, the use of DIFLUCAN in nursing mothers is not recommended.

Pediatric Use
Efficacy of DIFLUCAN has not been established in children. A small number of patients from age 3 to 13 years have been treated safely with DIFLUCAN using doses of 3-6 mg/kg daily.

The safety and effectiveness of DIFLUCAN 150 mg tablets in the treatment of vaginal candidiasis in patients under 18 years of age have not been established.

Adverse Reactions
In patients receiving a single dose for vaginal candidiasis,

During comparative clinical studies conducted in the United States, 448 patients with vaginal candidiasis were treated with DIFLUCAN, 150 mg single dose. The overall incidence of side effects possibly related to DIFLUCAN was 26%. In 422 patients receiving active comparative agents, the incidence was 16%. The most common treatment-related adverse events reported in the patients who received 150 mg single dose fluconazole for vaginitis were headache (13%), nausea (7%) and abdominal pain (6%). Other side effects reported with an incidence equal to or greater than 5% included diarrhea (1%), dyspepsia (1%), headache (1%), and taste perversion (1%). Most of the reported side effects were mild to moderate in severity. Rarely, anaphylactic and anaphylactoid reactions have been reported in marketing experience.
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[Advertorial Content]

DDAVP® Nasal Spray (desmopressin acetate) 5mL

BRIEF SUMMARY
CONTRAINdication: Known hypersensitivity to DDAVP Nasal Spray.

WARNINGS:
1. For intranasal use only.
2. Do not use in young and elderly patients in particular. Fluid intake should be adjusted downward in order to decrease the potential occurrence of water intoxication and hyponatremia. Particular attention should be paid to the possibility of the occurrence of an extreme decrease in plasma osmolality that may result in seizures which could lead to coma.

PRECAUTIONS:
General: DDAVP Nasal Spray at high dosage has infrequently produced a slight elevation of blood pressure which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.

Pharmacology: DDAVP Nasal Spray should be used with caution in patients with conditions associated with fluid and electrolyte imbalance, such as cystic fibrosis, because these patients are prone to hyponatremia. Rare severe allergic reactions have been reported with DDAVP. Anaphylaxis has been reported with intranasal administration of DDAVP, but not with DDAVP nasal.

Central Cerebral Diabetes Insipidus: Since DDAVP Nasal Spray is irritant in the naso mucosa submucosa, nasopharynx, or oropharynx, it should not be used in patients with central diabetes insipidus in which stimulation of ADH synthesis results in nausea in patients with no harm to the fetus reported; however, no controlled studies in pregnant women have been conducted. Reports stress that, as opposed to oral preparations containing the natural hormone, DDAVP Nasal Spray (desmopressin acetate) in antidiuretic doses has no uterotonic action, but the patient will have to weigh possible therapeutic advantages against possible dangers in each individual case.

Nasal Absorbers: There have been no controlled studies of the effect of intranasal dose of 0.1 mg in normal volunteers.

Pediatric Use: DDAVP Nasal Spray has been used in childhood and moderate enuresis. See also comments on DDAVP nasal in the above sections. It has been shown to be safe and effective in children aged 6 years or older with childhood nocturnal enuresis. Adequate controlled studies with DDAVP Nasal Spray in primary nocturnal enuresis have not been conducted beyond 4-6 weeks. The dose should be reduced gradually to achieve the best therapeutic effect. Since the spray cannot deliver less than 0.1 mL (10 mg), smaller doses should be administered using the nasal tube delivery system. Do not use the nasal spray in pediatric patients requiring less than 0.1 mL (10 mg) per dose. The results of an occasional change in response with time, usually greater than 6 months, some patients may show a decreased responsiveness, a shortened duration of effect. There is no evidence this effect is due to the development of antibodies but rather may be a result of habituation. Adverse reactions have also been reported.

ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally with mild abdominal cramps. These symptoms are disappeared with reduction in dosage. Rarely, cough and upper respiratory infections have also been reported.

The following table lists the percent of patients having adverse events without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

<table>
<thead>
<tr>
<th>ADVERSE REACTION</th>
<th>PLACEBO (N=29)</th>
<th>DDAVP 20 mcg (N=66)</th>
<th>DDAVP 40 mcg (N=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body As A Whole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Throat Irritation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NERVOUS SYSTEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RESPIRATORY SYSTEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nasal Pain</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nasal Irritation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CARdioVASCULAR SYSTEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DIETETIC SYSTEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorder</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SKIN &amp; APPENDAGES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SPEcial senses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Excoriation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Laxation Disorder</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

OVERDOSAGE: See adverse reactions above. In case of overdose, the dose should be reduced, frequency of administration decreased, or the drug withheld according to the severity of the condition. There is no known specific antidote for DDAVP Nasal Spray. An oral LD50 has not been established. An intranasal dose of 2 mg/kg in mice demonstrated no effect.

CAUTION: Federal U.S.A law prohibits dispensing without prescription. Please see product circular for full prescribing information.

REFERENCES:

Manufactured for

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- Significant improvement in number of dry nights shown in controlled studies
- Rapid response—substantial effect seen in as few as 1 to 3 nights of treatment
- A combined 15-year record of successful and safe use in the U.S. and Europe

Nighttime fluid intake should be restricted to decrease the potential occurrence of fluid overload; serum electrolytes should be checked at least once when therapy is continued beyond 7 days.

DDAVP® Nasal Spray
(desmopressin acetate) 5mL

Dry Nights for Good Mornings

Please see brief summary of prescribing information on adjacent page.
Living in Medicine

The Green Bag
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Therapy for Attention-Deficit Hyperactivity Disorder
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In Reply
Daniel C. Vinson, MD, MSPH

Science and Technology

Environmental Tobacco Smoke: Health Effects and Prevention Policies
Council on Scientific Affairs, American Medical Association

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For some of your patients, this list could be a life saver.

- Feelings of sadness or irritability
- Loss of interest or pleasure in activities once enjoyed
- Changes in weight or appetite
- Changes in sleeping pattern
- Feeling guilty, hopeless or worthless
- Inability to concentrate, remember things or make decisions
- Fatigue or loss of energy
- Restlessness or decreased activity
- Complaints of physical aches and pains for which no medical explanation can be found
- Thoughts of death or suicide

This list of symptoms is being featured in a print ad as part of the National Mental Health Association's (NMHA) National Public Education Campaign on Clinical Depression. The campaign communicates these basic messages: Clinical depression is a medical illness. Effective treatments are available. See a doctor. A free booklet on clinical depression is available by calling NMHA at 1-800-228-1114.

The National Public Education Campaign on Clinical Depression is being co-sponsored by the American Medical Association along with nine other national professional health and mental health associations.

National Mental Health Association...
INTRODUCING

BRONTEX

THE COUGH LIQUIDATOR

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.

3 times more guaifenesin per tablet than a teaspoon of other codeine brands.*
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.

FROM THE MAKERS OF ENTEX® PRODUCTS

NEW Brontex®

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

GUAIFENESIN........300 mg

FEWER COUGHS, WETTER COUGHS

Please see brief summary of prescribing information on next page.
A 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.
* Recommended dosing for most codeine/guaifenesin products is two teaspoons every four hours.

**Bronutex® (codeine phosphate/guaifenesin) tablets

**DESCRIPTION:** Each Bronutex® tablet and 4 teaspoons (20 mL) of Bronutex 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 inhaled irritants. Helps loosen phlegm (mucus) and thus bronchial secretions to aid the bronchial passages of mucus-removing inclusions.

**CONTRAINDICATIONS:** Bronutex tablets are contraindicated in patients with known hypersensitivity to any of its ingredients. Bronutex tablets are contraindicated for use in patients with asthma.

**WARNINGS:** Codeine is not recommended for use in children under 12 years of age. Children under 12 years may be more susceptible to the respiratory depressant effects of codeine, including respiratory arrest, coma, and death.

**PRECAUTIONS:** Guaifenesin should be used with extreme caution in patients with severe CNS depression, respiratory depression, or those prone to respiratory depression, such as alcoholics, chronic pulmonary disease and those with substantially decreased respiratory reserve. Codeine should be administered in caution with 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 very young or elderly or debilitated patients.

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

Delele of codeine should not be increased if cough fails to respond; an separate cough should be nevaluated in 5 days or sooner for underlying pathology, such as foreign body or lower respiratory tract disease. Codeine may cause or aggravate constipation.

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

**Head Injury and Increased Intracranial Pressure:** The risk of respiratory depression and elevation of intracranial fluid pressure is increased by codeine, including codeine, in the presence of head injury, intracranial lesions, or a preexisting increase in intracranial pressure. They also may produce adverse reactions such as sweating and primary change which may obscure the clinical course of patients with head injuries.

**Respiratory Conditions with Productive Cough or Chronic Respiratory Disease:** The risks and benents of codeine or guaifenesin in these patients may be involved in cases associated with productive cough or chronic respiratory disease when improved with a clear bronchial obstruction of secretions may be a deten
tious effect on the patient's respiratory function.

**Information for Patients:** Bronutex tablets may cause marked drowsiness or may impair the mental and 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 clear to them that they do not become drowsy or sleepy from Bronutex tablets. Patients should be supervised to avoid potential harm in riding bicycle or other hazardous activities.

**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 Interrelations:** Guaifenesin has been reported to interfere with clinical laboratory determinations of urinary 2-hydroxypropiolic acid and urinary hydroxyurea (VMA) because codeine may decrease urinary excretion of certain drugs by decreasing the rate of renal excretion. codeine may be eliminated more slowly in patients with impaired renal function.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Studies with Bronutex tablets in animals to evaluate carcinogenic, mutagenic, or teratogenic 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 Bronutex tablets. It is also not known whether Bronutex tablets causes fetal harm when administered to a pregnant woman or can affect reproduction capacity. Bronutex tablets should be given to a pregnant woman only if clearly needed.

Studies with codeine in hamsters and mice to evaluate its teratogenicity potential have not 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 anomalies.

**Nonteratogenic Effects:** Depression 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 effects are usually self-limiting and resolve within days or weeks following discontinuation of the drug. In severe cases, treatment with codeine may be considered for codeine-exposed in breast milk in individuals causing codeine should be considered.

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

**ADVERSE REACTIONS:**

**Contraindications:** CNS depression, particularly respiratory depression, light-headedness, dizziness, exsanguination, epistaxis, dizziness, headache, transient hallucination, disorientation, visual disturbances, and convulsions.

**Drug Abuse and Dependence:** Bronutex tablets are a Schedule IV controlled substance. Bronutex liquid is Schedule IV controlled substance.

**Drug Interactions:** Bronutex should be used with caution in patients with a history of drug abuse or dependence. Psychopharmacological dependence, physical dependence, and tolerance are known to occur with codeine.

**OVERDOSE:**

**Signs and Symptoms:** Serious overdose with codeine is characterized by respiratory depression (a decrease in respiratory rate, interval volume, Cheyne-Stokes respiration, cyanosis), extreme sleepiness progressing to stupor or coma, cyanosis (may occur in terminal moribund), skeletal muscle fasciculation, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, a mononuclear cell or circulatory collapse, cardiac arrest and death may occur.

**Treatment:** The treatment of overdose 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 controlled or ventilatory ventilation as necessary. The tachy-arrhythmic reaction of the heart is a specific antidote against respiratory depression resulting from overdose or unusual sensitivity to spasmology, including codeine. Therefore, an appropriate dose of naloxone hydrochloride should be given. In cases of severe respiratory depression, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

**Antidepressant:** Bronutex should not be used 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 presenting emergency is considered dangerous or excessive, induce vomiting with ipecac syrup unless the patient is vomiting, convulsing, 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 catheter.

**Dosage and Administration:**

**Adults and Children:** 12 years of age and older: one tablet every 4 hours. Bronutex tablets are not recommended for children under 12 years of age.

**Liquid:** Adults and children 12 years of age and older: 4 teaspoons every 4 hours. Children 6 to 12 years of age: 2 teaspoons every 4 hours.

**How Supplied:**

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

**NC**: 49-044-0041-01 bottle of 100

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

**CAUTION:** Federal law prohibits dispensing without prescription.

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A Little Means A Lot To The Older Hypertensive

Comparable antihypertensive efficacy to 2.5 mg* with the safety profile of a lower once-daily dose

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Safe and effective for step-down therapy

Side-effect profile compatible with other antihypertensive agents

LOZOL 1.25 mg once daily is now the recommended starting dose for indapamide in hypertension

LOW-DOSE ONCE-DAILY

INDAPAMIDE TABLETS

INDICATIONS: LOZOL (indapamide) is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs, and for the treatment of salt- or volume-dependent edema (e.g., congestive heart failure). Usage in Pregnancy: See PRECAUTIONS.

CONTRAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamides.

WARNINGS: Inefective cases of severe hypotension accompanied by hypokalemia have been reported with 2.5 mg and 5.0 mg indapamide primarily in elderly females. Symptoms were reversed by electrolyte replacement. Hypokalemia caused possibly clinically significant (125 mEq/L) has not been observed in controlled trials with the 1.25 mg dosage (see PRECAUTIONS). Hypokalemia occurs commonly with diuretics (see ADVERSE REACTIONS, hypokalemia), and electrolyte monitoring is essential. In general, diuretics should not be given concomitantly.

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are sodium-restrictive or receiving potassium fluids, in patients subject to electrolyte imbalances, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalances such as hypokalemia, hyperkalemia, acidosis, or alkalosis. The risk of hypokalemia secondary to diuresis and renins is increased with larger doses, with the elderly, with severe cardiac, and with concurrent use of corticosteroids or ACTH. Intolerance with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can ameliorate the response of the heart to the toxic effects of digitalis, such as increased intracellular instability. Diastolic hypotension may occur in sensitive patients; appropriate treatment is usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually not required specific treatment except in extraordinary circumstances (liver, renal diseases). Thiazide-like diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Hypokalemia may occur, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should be monitored periodically.

Use with caution in patients with severe renal disease; consider withholding or discontinuing if progressive renal impairment is observed. Renal function tests should be performed periodically.

Use with caution in patients with impaired hepatic function or progressive liver disease; since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

In patients with mild or moderate hypertension, a 4-week, single-blind placebo washout period was followed by an 8-week, open-label treatment period with LOZOL 2.5 mg. Patients responding to single-blind, randomized treatment with either LOZOL 2.5 mg or LOZOL 1.25 mg. Treatment success was defined as a decrease in supine diastolic blood pressure to 90 mm Hg or less by week 8 of the double-blind period.

* Because of the diuretic effects of LOZOL 1.25, changes in certain electrolytes and blood chemistries can occur. Serum electrolytes and blood chemistries should therefore be monitored.

+ 19.6% of patients had values less than 3.4 mEq/L. Only 7.5% had potassium levels below 3.2 mEq/L and less than 1% fell below 3.0 mEq/L. Metabolic changes at higher doses of indapamide may be greater.

As in all step-down therapy, the patient should be monitored for maintenance of blood pressure control.

Please see brief summary of prescribing information below.
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receiving methylphenidate and in four (11%) while receiving placebo, a highly significant difference statistically and clinically.” In contrast, Mattes et al.12 concluded that:

No overall benefit from methylphenidate was evident, regardless of childhood history of ADD-H [attention-deficit disorder with hyperactivity]. Approximately 25% of the sample appeared clinically to benefit from methylphenidate. . . . Even among the responders, benefits was generally not as marked nor as clinically valuable as in childhood ADD-H.

We need to define the prognosis of ADHD as seen in primary care and the spectrum of adverse outcomes in a way that is generalizable to primary care practice. Further controlled clinical trials are needed to define the appropriate pharmacological and psychological treatment of ADHD in adults, as well as in children, and to identify which treatments in children with ADHD lead to improved outcomes in adulthood.

Daniel C. Vinson, MD, MSPH
University of Missouri
Columbia

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OR ANGINA
IN HYPERTENSION OR ANGINA

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In hypertension¹

- The magnitude of blood pressure reduction is related to the degree of hypertension
- Low incidence of vasodilatory side effects
- No reflex tachycardia is associated with chronic antihypertensive effects

In angina¹

- Potent dilator of coronary arteries* and reduces vasospasm
- Appropriate decrease in heart rate with a low incidence (<1%) of reflex tachycardia
- Little or no negative inotropic effect in patients with normal ventricular function†

WELL-TOLERATED CONTROL REGARDLESS OF AGE OR GENDER‡

- A side-effect discontinuation rate comparable to placebo in both hypertension and angina trials²

- 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%)³

* Demonstrated in patients with vasospastic angina.
† See Warnings and Clinical Pharmacology sections in prescribing information.
‡ In clinical trials with Cardizem CD.

Please see brief summary of prescribing information on next page.

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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
hypersensitivity to diltiazem or any of its components, and (5) patients with acute myocardial infarction and pulmonary compromise
documented by rales 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 rate. A study in patients with sick sinus syndrome, suggested that up to one-third,
(11% of 3090 patients or 0.4%). Concurrent use of digoxin with beta-blockers or digitalis may result in additive
effects on cardiac conduction. Administration of Cardizem to patients with Prinzmetal’s variant angina periods of systole (2 to 5 seconds) after a single dose of 60 mg of digoxin.

2. Congestive Heart Failure: Although diltiazem has a negative inotropic effect in isolated animal tissue prepara-
tions, pharmacologic studies in humans do not clearly support a negative inotropic effect. Nonetheless, Cardizem
is indicated for the treatment of angina and hypertension. The use of Cardizem in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

4. Acute Hepatic Injury: Mild elevations of transaminases with and without concurrent elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved with continued dilution of therapy. In rare instances, significant elevations in enzymes of hepatic function have been observed, and in certain cases with fatal outcome. Cardizem therapy may occasionally result in symptomatic hypotension.

5. Acute Hepatic Injury: Mild elevations of transaminases with and without concurrent elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved with continued dilution of therapy. In rare instances, significant elevations in enzymes of hepatic function have been observed, and in certain cases with fatal outcome. Cardizem therapy may occasionally result in symptomatic hypotension.

ADVERSE REACTIONS

Cardizem (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. Cardizem (diltiazem hydrochloride) is substantially and variably absorbed following oral administration. The degree of absorption is highly variable and is dependent on the formulation. Cardizem is metabolized in the liver by CYP3A4 and CYP2C19.

Cardizem and its metabolites are excreted in the urine and are not dialyzed.

Cardizem is primarily excreted in the urine as metabolites. Cardizem is a substrate for CYP3A4 and CYP2C19. The most common adverse reactions reported in clinical trials of Cardizem SR capsules involving over 1000 Cardizem SR capsules, including those with cardiac events (e.g., sudden cardiac death) were asthenia (6%), headache (4.5%), dizziness (3.5%), asthma (2.9%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1%), nausea (1%), and pain (1%).

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, vegetable extralysates
Nervous System: Abnormal dreams, anxiety, depression, gait abnormality, hallucinations, insomnia, nervousness, personality change, paresthesia, tremor, tinnitus
Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysphagia, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase ( EXTRA-HEPATIC LIVER DISEASE), pyrosis, vomiting, weight increase
Dermatological: Feltchyes, photosensitivity, pruritus, urticaria
Other: Arthralgia, CPK increase, dyspnea, eosinophilia, eye irritation, hypotension, hyperhidrosis, hypertension, impotence, muscle cramps, nasal congestion, rhabdomyolysis, prophylactic, allergy, cardiovascular, drug reaction, dyspnea, edema, fever, flushing, headache, hypotension, hypokalemia, hypotension, palpitations, paresthesia, pruritus, rash, tachycardia, urticaria, vomiting, weight increase

Cardizem therapy may occasionally result in symptomatic hypotension.


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*(felodipine)* Tablets, 5 mg, 10 mg

Because you consider the whole patient.

*1993 IMS NDTI Prescription Data.
†Peripheral edema, generally mild, was the most common adverse event in clinical trials.
PLENDIL is contraindicated in patients who are hypersensitive to this product. Please see brief summary of Prescribing Information on page following next page.
**PRECAUTIONS**

**Geriatric: Imitation:** Felodipine, like other calcium antagonists, can occasionally precipitate significant hypotension and rarely syncpe. It may lead to reflex tachycardia which in susceptible individuals may precipitate angina. **INTERACTIONS:**

**Heart Failure:** Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with felodipine have not demonstrated notable negative inotropic effects, safety in patients with heart failure has not been established. Caution therefore should be exercised when using felodipine in patients with heart failure or concomitant use of ventricular pacemakers, particularly in combination with a beta blocker.

**Elderly Patients or with Impaired Liver Function:** Patients over 65 years of age or patients with impaired liver function may have decreased plasma concentrations of felodipine and therefore may require lower doses of PLENIL. These patients should have their blood pressure monitored closely during dosage adjustment of PLENIL and should rarely require doses above 10 mg. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections of complete prescribing information.)

**Peripheral Edema:** Peripheral edema, generally mild and not associated with generalized fluid retention, was the most common adverse event in patients receiving felodipine. Peripheral edema was observed in 10% of patients. There have been some reports that felodipine can cause swelling in the esophageal region. These reports are probably due to the well-known swallowing disorders that can occur with any drug which requires swallowing.

**Frequency:** In a 2-year carcinogenicity study in rats fed felodipine at doses of 75, 150, or 300 mg/kg/day up to 28 times the maximum recommended human dose on a mg/m2 basis, a dose related increase in the incidence of benign interstitial cell tumors of the testes ( Leydig cell tumors) was observed in treated male rats. These tumors were not observed in a similar study in mice at doses up to 138.6 mg/kg/day (26 times the maximum recommended human dose on a mg/m2 basis). These Leydig cell tumors were considered to be hormonally induced, as they have been shown to lower testosterone production and to produce a corresponding increase in serum luteinizing hormone in rats. The Leydig cell tumors developed in an estrogen analog-like manner, but these hormonal effects which have not been observed in man.

In this same rat study a dose-related increase in the incidence of focal squamous cell hyperplasia compared to control was observed in the esophageal gland of male and female rats in all dose groups. No other drug-related esophageal or gastric pathology was observed in the rats or with chronic administration in mice and dogs. The latter is regulated trademark of Astra AB

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For more information about the AMA Interim Meeting or joining the AMA-RPS, contact the AMA Department of Resident Physicians Services at 312/464-4751.

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Calan® SR (verapamil hydrochloride)

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see Warnings), hypotension (systolic pressure < 90 mm Hg) or cardiac shock, sick sinus syndrome if no pacemaker is present, 2nd or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (e.g., WPP or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction or ventricular arrhythmia. If atrial flutter/fibrillation occurs, treatment with a beta-blocker is recommended. If the arrhythmia persists, further management should be individualized. Elevation of liver enzymes has been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (e.g., WPP or LGL syndromes) have developed an increased irregularity of the atrial assessment. In patients with atrial flutter/fibrillation after receiving IV. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV node block may occur in 2nd- and 3rd-degree (0.8%) development of heart block or progression to 2nd- or 3rd-degree block requires reduction in dosage or rarely, discontinuation and institution of appropriate therapy. Sustained ventricular tachycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertensive cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (if severe dysfunction is present). Unlike heart disease, heart rate should be reduced and patients should be monitored for abnormal prolongation of the QT interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent succinylcholine. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, antimuscarinic and/or beta-blocking activity. In those with congenital heart block, verapamil may reduce total body clearance and extracardiac clearance of digoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Digoxin in amida should not be given within 48 hours before or after 24 hours after verapamil administration. Concomitant use of furosemide and verapamil may have additive effects on myocardial contractility. AV conduction, and reperfusion. Combined verapamil and quinidine therapy in patients with hypertensive cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in increased sensitivity to lithium (toxicosis), with either no change or an increase in serum lithium levels; however, this may also result in a decrease in serum lithium levels. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of digoxin, and verapamil inhibits the clearance and increase the plasma levels of theophylline. Concomitant use of digitalis glycosides and colic enemas needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (uracil-like and depolarizing) and dose reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a teratogenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequately and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk, therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (0.2%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50 mm Hg (1.4%), AV block: total 1°, 2°, 3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1% or less of patients, occurred under conditions where a causal relationship is uncertain: anaphylactic shock, antineutrophilic dissociation, chest pain, claudication, myocardial infarction, pancytopenia, peripheral neuropathy, syncope, tachycardia, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, carotid artery stenosis, angina, and/or myocardial infarction, increased urination, swelling, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gnathostoma, gingivitis, hyperglycemia, hirsutism, increased urination, urinary incontinence, impotence.

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The recommended starting dosage for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control. A lower starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients of small stature). Dosages above 240 mg daily should be administered in divided doses. Calan SR should be administered with food. Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR. Verapamil should be administered cautiously to patients with impaired renal function.

Please see following page for brief summary of complete prescribing information.

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